is to reduce the generation of nitrogen oxides during combustion and to remove the particlulate matter from the exhaust stream.

Some of most promising devices for removing the particulate matter employ a filter to trap the particles; loaded traps are then regenerated by burning off (oxidizing) the accumulated particles. A number of different traps have been developed for filtering diesel exhaust; among these, the ceramic monolith trap appears to have the most useful characteristics. Several approaches have been used for regenerating the ceramic filters; the most promising among these appears to be the use of metallic fuel additives, such as organomanganese compounds. Such compounds reduce the combustion temperature of the particles trapped on the filter, so that they burn off at the temperature of the exhaust. The use of such fuel additives is likely to increase the ambient levels of manganese (Mn), particularly in urban areas.

This report focuses on health issues in the context of increased public exposure to manganese from diesel-fueled vehicles using a trap and manganese fuel additive to reduce particulate emissions. The objectives of this report are (1) to review information on the health effects associated with manganese, (2) to review information on the likely exposure to manganese from its intended use, and (3) to evaluate whether or not the increased ambient levels of manganese might be expected to produce adverse health effects.

As far as the Health Effects Institute (HEI) has been able to determine, no automobile or engine manufacturer is planning to implement manganese-based technology to reduce

particulate emissions in the near future; an earlier attempt by Volkswagen in this direction has been abandoned. Therefore, at this time, HEI has not reviewed and analyzed the manganese issue as extensively and exhaustively as it did in the case of methanol and gasoline vapors. HEI efforts in this direction were hampered by the paucity of information on the nature of manganese products emitted from the tailpipes of vehicles using the manganese technology. If the use of manganese fuel additives in the United States becomes a reality, and if more information on manganese emissions becomes available, HEI will be ready to undertake a more comprehensive analysis of the information and, if necessary, undertake appropriate research.

HEI Involvement

In a letter to the Health Effects Institute (HEI), dated June 29, 1984, Volkswagen of America, Inc., requested the HEI to undertake an evaluation of potential health issues related to emissions from diesel automobiles using manganese-containing fuel additives for particle-trap regeneration (Attachment A). On October 7, 1985, the Health Effects Institute responded to the Volkswagen request in a letter (Attachment B).

The HEI letter concluded: "The available data do not indicate that currently anticipated levels of manganese emissions from diesel automobiles using Lubrizol 8220 are associated with increased public health risks." This conclusion was based on an analysis that followed the tenets for environmental health assessments. Thus, modeling data on projected scenarios of exposure to manganese emissions were evaluated together with the available data base on the health effects of manganese to determine whether exposures would

occur at or near hazardous levels. The discussion of health effects was based on both human epidemiologic and available toxicologic data.

In May 1986, the EPA asked HEI to clarify and amplify certain specific findings of HEI's report. The EPA also suggested that HEI undertake a research program on the health effects of low levels of manganese. The general issues of HEI's role in assessing the health effects of unregulated pollutants were elaborated in a memorandum to the record from Gray, Grumbly, and Maxwell, dated August 11, 1986 (Attachment C).

In the winter of 1986, HEI heard from Volkswagen that it was abandoning the use of manganese fuel additives and planned to switch to fuel additives containing other metals. In May 1987, the EPA reiterated its interest in receiving from HEI an evaluation of the health effects of manganese. This report has been prepared in response to that request.

Prior to the technical summary, we briefly discuss the statutory and institutional frameworks for our response.

Framework and Process

The evaluation of health effects of manganese is relevant both to the compliance of automobile manufacturers with the Clean Air Act and to the chartered role of the Health Effects Institute. Section 202(a)(4) of the Act states that "no emission control device, system, or element of design shall be used in a new motor vehicle or new motor vehicle engine for purposes of complying with standards prescribed under this subsection if such device, system, or element of design will cause or contribute to an unreasonable

risk to public health, welfare, or safety in its operation or function." The manganese additive in question is a key ingredient in a new technology designed to lower diesel particulate emissions in compliance with federal and California state laws. As such, this technology is covered by Section 202(a)(4) of the Clean Air Act.

The Health Effects Institute operates under the joint sponsorship of the EPA and the motor vehicle industry, and is structured to define, support, and review scientific research aimed at improving understanding of the possible health effects of mobile source emissions. In a letter dated March 20, 1984, to all motor vehicle and engine manufacturers, Joseph Cannon, the EPA Assistant Administrator for Air and Radiation, and Bernard Goldstein, the EPA Assistant Administrator for Research and Development, jointly reaffirmed the Health Effects Institute as "the primary mechanism through which participating motor vehicle manufacturers discharge their health testing responsibilities under Section 202(a)(4) of the Clean Air Act." They further urged "that unregulated emissions of potential importance be brought to the Health Effects Institute's attention in a timely manner."

It is in the context of meeting its obligation to its sponsors, and its role in helping to implement Section 202(a)(4) of the Clean Air Act, that the HEI has conducted an evaluation of the anticipated levels of ambient manganese from its use as a fuel additive, and of potential adverse health effects from such exposure.

BACKGROUND INFORMATION ON MANGANESE

Ambient Levels of Manganese

Manganese is the 12th most abundant element on earth and is found mainly in oxide or carbonate form as a natural constituent of soil and water. As such, manganese is a component of background aerosol that winds, waves, and other natural processes generate.

Monitoring of ambient manganese in the United States started in 1953. As a general trend, manganese levels have decreased since that time and have remained relatively stable since 1972. Improved industrial control processes are believed to account for much of the decrease. Quarterly data collected by the National Air Surveillance Network show that between 1972 and 1982 in urban sites, the highest median level of manganese for any year was 0.034 $\mu g/m^3$ (1978), and the highest 95th percentile level was 0.12 $\mu g/m^3$ (1972); corresponding values for non-urban NASN sites are a median of 0.009 $\mu g/m^3$ (1977) and 95th percentile of 0.030 $\mu g/m^3$ (1976, 1977) (U.S. Environmental Protection Agency 1984). These data, though valuable, are regional and tend to obscure the higher local manganese levels that may result, for example, from industrial activity, quarrying processes, or farming. For example, near foundries, manganese levels can typically reach 0.3 $\mu g/m^3$, and near ferromanganese plants, they can exceed 1 $\mu g/m^3$. EPA Storage and Retrieval of Aerometric Data (SAROAD) collected from 1980 to 1982 (Table 1) show that many areas experience peak 24-hour manganese levels in excess of 0.1 $\mu g/m^3$, and that locations in Indiana, Maryland, and Pennsylvania registered mean 24-hour averages greater than 0.1 $\mu g/m^3$.

The highest exposures to airborne manganese occur occupationally in mining operations, ore-processing plants, and ferromanganese plants (Table 2). The levels in these settings may be higher by a thousand times or more than the ambient urban levels discussed earlier. In recognition of the potential toxicity of manganese at these extreme occupational levels, workplace standards have been set (Table 3). At 300 $\mu g/m^3$ time-weighted average, the World Health Organization has the most stringent standard. In interpreting the meaning of this level, it is important to bear in mind that a workplace standard applies to a workforce that is presumed healthy and more resilient to environmental insults than the population at large. Workplace standards are not applicable to the general public and should not be construed as protective of the public's health.

Dietary Intake and Body Burden

Manganese is classified as essential for normal physiologic functions, such as skeletal development and reproduction. It is a necessary activator or cofactor of numerous enzymes and is especially concentrated in tissues rich in mitochondria. Average adult dietary intake of manganese is about 3 to 4 mg per day (usual range 2 to 9 mg/day) resulting in a steady-state body burden of 12 to 20 mg for a 70 kg person (National Research Council 1973). This manganese is distributed throughout the body's tissues as shown in Table 4. Manganese-deficient states have been described for several mammalian species.

Manganese is found in a wide variety of foods (Table 5), and food accounts for at least 98 percent of an adult person's daily intake of manganese, with practically all the remainder in beverages. Inhalation, in all but the most

polluted occupational settings, contributes negligibly to the body burden of manganese.

Despite the variability in the daily ingestion of nutrients, homeostatic mechanisms maintain tissue manganese concentrations at relatively stable levels. This control is exercised primarily by regulation of intestinal absorption and biliary excretion of manganese (Abrams et al. 1976; Klaasen 1974).

Under normal circumstances, humans absorb roughly 3 percent of ingested manganese across the intestinal wall, with the rest passing into the feces (Mena et al. 1969); similar uptake has been reported in experiments on animals (Greenberg et al. 1943; Pollack et al. 1965). Once across the intestinal wall, manganese is cleared rapidly (within several minutes) from the bloodstream and distributes throughout the body, the largest fractions usually delivered to liver and kidney (Cotzias et al. 1968; Cahill et al. 1980). Clearance of manganese from the body occurs in two phases: fast and slow. A study of humans injected intravenously with radioactive manganese chloride reports that approximately 70 percent of the injected activity was cleared in a slow phase with a half-time of 39 days; the fast component half-time was four days (Mahoney and Small 1968). Studies of mice have also shown two-phase clearance kinetics (Britton and Cotzias 1966). These phases may represent the dynamics of manganese utilization within tissues, but probably also reflect the highly variable turnover of manganese among tissues. For example, turnover of manganese is considerably slower in the brain than in the liver (Cotzias et al. 1968; Cahill et al. 1980; Rehnberg et al. 1980, 1981). Elimination of previously absorbed manganese is almost exclusively in the feces and is principally associated with biliary secretions (Klaasen 1974).

HEALTH EFFECTS OF MANGANESE

Being an essential element, manganese exhibits the deficiency-sufficiency-toxicity spectrum; the discussion in this report is focused on the toxicity end of this spectrum. The adverse health effects of manganese have been reviewed by several authors (Cooper 1981; Fraunhofer-Institut 1984) including an in-depth review by the EPA (U.S. Environmental Protection Agency 1984).

Administration of manganese compounds by subcutaneous, intraperitoneal, or intramuscular routes has induced tumors in some animal studies, but not in others (reviewed in U.S. Environmental Protection Agency 1984). There are no studies which have investigated whether inhaled manganese is carcinogenic in laboratory animals, and there is no epidemiologic information that sheds light on the carcinogenicity of manganese in humans.

The adverse health effects of greatest concern are neurotoxic and respiratory, and these have been reported over the past several decades in studies of occupational exposure to manganese. The vast majority of animal work has been conducted with oxides of manganese (which are insoluble), or $MnCl_2$ (soluble) administered by subcutaneous, intraperitoneal, or intramuscular routes; relatively little work has been done on the effects of exposure via the inhalation route.

Modifying Factors

Before discussing the neurotoxicity or pulmonary toxicity of manganese, it is important to discuss briefly

several factors that modify the uptake and subsequent disposition of manganese. These factors are divided into six categories: the first two concern the quantities of manganese in the exposure and already in the subject; the next two involve the state of the subject; and the final two focus on the chemical and physical aspects of exposure, particularly the route of exposure. Though identified separately, they are, by nature, interrelated.

Dose administered: As the dose of manganese given orally (in oxide form) to laboratory animals increases, the percentage of absorption across the intestinal wall decreases (Cahill et al. 1980). Furthermore, as the dose of manganese given intraperitoneally or intravenously increases, the rate of biliary excretion also increases (Greenberg and Campbell 1940; Klaasen 1974). Thus, as mentioned previously, controlled absorption and excretion function to stabilize the body burden of manganese in the face of varying dose.

Preexisting Body Burden of Manganese: Experiments on animals and humans show that subjects with elevated dietary levels of manganese, or an occupational history of exposure to manganese, eliminate a radiolabeled intravenous or oral dose of manganese with shorter half-times than subjects with normal body burdens (Cotzias et al. 1968; Suzuki 1974; Abrams et al. 1976). Therefore, both incoming dose and existing body burden of manganese constitute important inputs to the mechanisms responsible for regulation of manganese levels in the body.

Age of Subject: The barriers to manganese transport that operate in adult rats at the intestinal wall, and at the blood-brain and blood-testes interfaces, are not yet fully developed in preweanling subjects. Consequently, manganese

accumulates in brain, testes, and other tissues of very young rats fed manganese-rich diets to a greater extent than it accumulates in the tissues of older animals (Kostial et al. 1978; Rehnberg et al. 1982). Homeostasis of manganese in the rat starts to become apparent during the third week of life, and over time, manganese levels return to normal (Cahill et al. 1980; Rehnberg et al. 1981). These findings suggest that human infants may accumulate manganese from dietary or other sources at rates higher than those observed for adults.

Diet and Nutritional Status: The whole body retention of manganese given orally as chloride to adult rats is over 100-fold higher when administered in a milk diet than when given in a standard diet (Kostial et al. 1978). Milk apparently stimulates manganese absorption and, in this regard, plays a "normal" role in its uptake during weaning. Another important factor that affects manganese uptake is iron deficiency. Interrelationships between this condition and manganese uptake are described in humans, but in more detail in laboratory animals (Pollack et al. 1965; Mahoney and Small 1968; Mena et al. 1974; Rehnberg et al. 1982). Briefly, iron-deficient states lead to increased absorption and distribution of manganese, and this effect may be especially pronounced in very young animals.

Manganese Species: Practically all experiments on manganese have employed either its oxide or its chloride form. Both forms are absorbed and distributed to the body's tissues but not necessarily in quantitatively equivalent manners. For example, in 8 to 12-day-old rats, the percentage of uptake of intubated Mn_3O_4 decreases dramatically with dose (down 17-fold when dose increases 50-fold) whereas the regulation of $MnCl_2$ is relatively moderate (down by 25 percent when dose increases 20-fold) (Cahill et al.

1980). Furthermore, the dispositions of the chloride and oxide forms differ following intratracheal administration, the chloride-associated manganese leaving the lung faster and appearing sooner in the feces (Drown et al. 1986). These differences are probably due, to a great extent, to the high aqueous solubility of manganese chloride and the relative insolubility of the oxide forms of manganese. One study shows that manganese oxides may partially solubilize within the acidic environment of lung macrophage phagosomes (Lundborg et al. 1984).

Route of Exposure: The preponderance of knowledge concerning the pathways leading from manganese uptake to excretion is based largely on feeding studies and to a lesser extent on studies using parenteral routes of exposure with particularly little information available on the inhalation route. One might expect that, since parenteral routes escape the initial "checkpoint" at the intestinal epithelium and subsequent direct entry into the portal circulation, the percentage of absorption and distribution of manganese following intraperitoneal injection or inhalation exceeds that following oral ingestion; on the basis of a limited number of studies, this, in fact, appears to be plausible (Mouri 1973; Kostial et al. 1978; U.S. Environmental Protection Agency 1984).

In summary, the total body burden of manganese is maintained by the regulation of intestinal absorption and biliary excretion; this equilibrium is affected by factors such as age (the young accumulate more), diet and nutritional status (iron-deficient individuals are more vulnerable), the chemical form of manganese, and the route of exposure.

Fate of Inhaled Manganese

The EPA's Health Assessment Document for Manganese states: "There are no quantitative data on absorption rates for inhaled manganese either in humans or in animals" (U.S. Environmental Protection Agency 1984). Up to that time, several inhalation studies using manganese aerosols had been performed on humans and animals, but had shed little light on subsequent disposition of the metal. In one study, humans exposed for 10 minutes to either chloride or oxide aerosols of radioactive manganese excreted between 40 and 70 percent of the activity within four days (Mena et al. 1969). Mice exposed to Mn_3O_4 aerosol for two hours cleared over 80 percent of the aerosol from the lung within a day, with increases of manganese in kidney and spleen noted by 48 hours (Adkins et al. 1980a).

For manganese inhaled as an insoluble oxide, the relative amounts of aerosol depositing in ciliated airways versus pulmonary regions will influence the characteristics of manganese clearance from the lung (Brain and Valberg 1979; Raabe 1982). Relatively "coarse" aerosols (3 to 5 μm) deposit primarily in the nose and upper airways and clear within a day directly to the gastrointestinal tract via the mucociliary lining; finer aerosols deposit in deeper lung regions--nonciliated bronchioles and alveoli--and are subject to slower clearance processes (weeks to years). A portion of the material deposited in the distal lung is sequestered into macrophages that eventually exit the lung on the mucociliary escalator; a fraction of macrophage-associated Mn oxides may also solubilize (Lundborg et al. 1984). The remainder stays associated with lung tissue or eventually enters the blood or lymph. The model of the Task Group on Lung Dynamics predicts that, for particles with long-term lung retention (weeks to

years), 5 to 20 percent of the material initially deposited in the pulmonary region will ultimately enter the circulation (in Stuart 1984).

The fate of radiolabeled manganese in both oxide and chloride forms after intratracheal instillation in rats was followed in a study by Drown and coworkers (1986). Intratracheal instillation is a method that probably favors delivery of material to the lung's alveolar region, and thus optimizes particle entry into compartments with long-term retention (Brain et al. 1976). For manganese instilled as an oxide, roughly 50 percent cleared the lung by three days after instillation, 70 percent by seven days, and over 90 percent by 14 days; after 14 days the lung burden of instilled manganese remained relatively constant. Consistent with its much higher aqueous solubility, manganese instilled as a chloride cleared from the lung four times as fast as the oxide in the first week, and from 14 days forward it remained in the lung at about the same concentration as manganese given as oxide. Accordingly, the radioactivity from manganese as chloride reached peripheral tissues more rapidly than from manganese as oxide. Despite apparently different kinetics of initial absorption, manganese instilled in soluble (chloride) and insoluble (oxide) forms attained remarkably equivalent tissue-specific levels, suggesting that, for the conditions of the experiment, both forms of manganese were subject to quantitatively (if not qualitatively) similar regulatory mechanisms. Half the manganese given as oxide was excreted in the feces in seven days and half given as chloride was excreted in three days. At two weeks 60 percent of the "oxide" and 70 percent of the "chloride" were excreted. By the fifth day, however, daily excretions of the two forms were equivalent, a trend that continued to 90 days, the final time point recorded.

Clearance rates of manganese from tissue were characteristic of individual tissue type; for example, clearance from brain was much slower than clearance from liver or kidney.

The experiments described together with the discussion of lung clearance indicate that, within days to several weeks of exposure, a substantial portion (at least 60 to 70 percent) of manganese particulate entering the respiratory tract is destined for clearance directly into the gastrointestinal tract. Under normal circumstances, 3 percent of this manganese is absorbed across the intestinal wall. The remainder undergoes processes with longer time constants, either clearing within macrophages to the gastrointestinal tract, entering the pulmonary circulation, or remaining indefinitely in lung tissue.

Neurotoxic Effects

The neurotoxic effects of manganese have been described in occupationally exposed populations. The neurotoxic effects may appear after a few months of manganese exposure, although they generally require two to three years of exposure. The early stages of manganese intoxication are accompanied by anorexia (loss of appetite), by asthenia (weakness), and occasionally by psychotic behavior. Headaches and leukopenia (decrease in the number of leukocytes in the blood) may also be found. At later stages, slurred speech, stolid mask-like appearance of the face, spastic gait-like disorder, tremor, lack of coordination, and emotional disturbance are also found. The symptoms of manganism resemble those of Parkinson disease and other diseases involving the extrapyramidal motor system (a functional unit of the central nervous system that is involved in the control of certain motor functions, such as posture,

support, and locomotion). However, manganism can be distinguished from Parkinson disease in that the former affects mainly the striatum and pallidum while the latter affects the substantia nigra (Mena et al. 1967; Cooper 1984; U.S. Environmental Protection Agency 1984).

Most reports from human clinical and epidemiologic studies suggest that the neurotoxic effects are not obvious until exposure exceeds 5 mg Mn/m^3 (or 5,000 μg Mn/m^3). A few studies have reported neurologic effects of manganese at lower levels of exposure. In a recent cross-sectional epidemiologic study, composed of 141 manganese-exposed workers and 104 control workers, Roels et al. (1987a) studied numerous indicators of the workers' health. The investigators reported significant alterations in several psychomotor tests (visual reaction time, audio-verbal short-term memory capacity, and hand tremor), and concluded that "a time-weighted average exposure to airborne manganese dust of about 1 mg/m^3 (1,000 $\mu g/m^3$) or less for 20 years or less may present preclinical signs of intoxication."

To date, Saric et al. (1977) have reported adverse neurologic effects at the lowest levels of exposure. They compared the neurologic symptoms among 369 workers from a ferroalloy plant (ambient concentration 0.3 to 20.4 mg Mn/m^3), 190 workers from an electrode plant (2 to 30 μg Mn/m^3), and 204 workers from an aluminum rolling mill (0.05 to 0.07 μg Mn/m^3), the last to serve as control subjects.

The subjective symptoms reported by the workers, such as bad mood, sleepiness, irritability, tremor, and stiff and tired legs, were not very specific and were found in a relatively high percentage of workers in all groups including the control group from the aluminum rolling mill. The smokers

from the ferroalloy group appeared to report some of the subjective symptoms more often than the smokers from the other groups.

An analysis of the neurologic signs among the workers showed that 17 percent of the workers in the ferroalloy plant had neurologic symptoms, as compared to 6 percent of the workers in the electrode plant and 0% of those in the aluminum plant. The most commonly observed neurologic sign was tremor at rest. The neurologic symptoms were not correlated with smoking. The workers from the ferroalloy plant were also subdivided into three groups according to the mean workplace manganese concentration. Although a statistically significant relationship between manganese concentration and neurologic signs was not found, the authors reported that "the number of neurological signs was ... rather numerous" in the least exposed group of workers (manganese concentrations between 0.301 and 4.933 mg/m^3). It should also be noted that the authors did not report whether or not there was an association between symptoms and the duration of exposure.

Thus, the study by Saric et al. (1977) suggests an effect of manganese between 0.3 and 4.9 mg/m^3. This study, however, suffers from several shortcomings. The most prevalent neurologic symptom, namely, tremor at rest, is not attributable solely to manganese. Possible confounding factors such as lead or other metals, or alcoholism, were not examined. In addition to manganese compounds, carbon monoxide, carbon dioxide, and coal dust were present in the factories. The study also suffers from other problems such as insufficient documentation of occupational histories and duration of exposure, and the methods applied for neurologic examination. There is also an unexplained inconsistency in the results: while the subjective symptoms appeared to be

correlated with a smoking habit, the neurologic signs were not.

Animal studies shed little additional light on the subject. The rat and other rodents do not develop the full spectrum of symptoms of manganese toxicity and, therefore, are not appropriate for such studies. Primates develop the manifestations of extrapyramidal disease and can be used for experimental studies. However, the chronic neurotoxicology studies reported in the literature have been inconsistent in themselves, and it is not possible to obtain reliable dose-response information from them (U.S. Environmental Protection Agency 1984).

In conclusion, neurotoxic effects of manganese have been extensively documented in individuals exposed to high levels of manganese. The use of manganese as a fuel additive is expected to result in fairly low ambient levels of manganese. An epidemiologic study has reported neurotoxic effects of manganese at low levels (Saric et al. 1977). While serious concerns remain regarding the interpretation of this study, it suggests that the lowest level at which the neurotoxic effects of manganese are observed may be in the range of 0.3 to 4.9 mg/m^3.

Pulmonary Toxicity

The respiratory effects of manganese involve an inflammatory effect or pneumonitis, which may lead to diminished pulmonary function, bronchitis, and altered susceptibility to infection. The respiratory effects of manganese are considered to be the health effect of most concern because respiratory effects have been observed at levels lower than those reported for neurotoxicity.

Human Studies: The effects of manganese on the respiratory system have been extensively documented in occupationally exposed populations. Workers exposed to high levels of manganese (1 mg/m^3 or greater) are at risk of developing pneumonia and chronic bronchitis. Effects of low levels of manganese (less than 0.4 mg/m^3) are not as well characterized, but it appears that workers exposed to such levels may not be at increased risk of pulmonary symptoms. Unfortunately, most studies in the literature do not describe the exposure levels in sufficient detail or precision to be useful in establishing an exposure-response relationship.

Populations living in the vicinity of manganese mines or factories have been studied to explore the health effects of exposure to lower levels of manganese. One such study has reported respiratory symptoms in children at very low levels of exposure. Nogawa et al. (1973) studied subjective symptoms and pulmonary functions in a population of junior high school students in Kanazawa city in Japan. The source of manganese was a ferromanganese plant. A cohort of 1,258 students classified as "exposed" attended a school 100 meters from the plant; 648 students in a school 7 km from the plant served as control subjects. Relative exposures of the two groups to manganese were determined by the amount of manganese in the dust fall at the two locations. Manganese concentrations were substantially higher around the plant than they were in the city; average levels around the plant were about 200 kg/km^2/month as compared to 8 kg/km^2/month or less in the city. The EPA estimated that the ambient levels of manganese in the vicinity of the Japanese plant were between 3 and 11 $\mu g/m^3$ (this was based on a comparison of the data from the Nogawa study with data from a ferromanganese plant in the Kanawah Valley in West Virginia) (U.S. Environmental Protection Agency 1984).

Participation of the students in the survey was nearly complete (98 percent). The authors concluded that students in the "polluted school" had a greater prevalence of sputum, nose, throat, and eye symptoms, and past history of pneumonia, than the students in the "control school." This observation was based on an analysis of subjective reporting of symptoms in the British Medical Research Council questionnaire. There were no reports of chronic bronchitis in either school. Several indicators of ventilatory functions (the forced expiratory volume, the one-second capacity, the one-second ratio, and the maximum expiratory flow) were lower in the students of the "polluted school" than in the students of the "control school." Also the one-second ratio of the students from the "polluted school" was lower the longer the students had been living in the polluted area and the nearer their homes were to the plant. Furthermore, the decline in the one-second ratio was comparatively greater among the students who had been attending the "polluted school" for a longer period of time (the upper grades). This suggested that the students were influenced both by the school atmosphere and by their home atmosphere. On the basis of these findings, the authors reached the conclusion that increases in subjective symptoms and decrements in pulmonary function seen in the students of the "polluted school" were associated with emissions from the ferromanganese plant, and that these effects could be readily explained in terms of manganese dust.

Several shortcomings in the Nogawa study cast serious doubts on the conclusions of the study. First, the reportedly greater prevalence of subjective symptoms among children at the polluted school is relatively modest; it is based on increased response to five questions out of more

than 40. Although the authors do not provide the details of the statistical methods they used, at p less than 0.05, the response to two out of 40 questions will be expected to be greater based on chance alone. Second, Nogawa et al. state that the pulmonary function of the students was measured at the "polluted school" during July 13-17,1970, and at the "control school" during July 22-24, 1970. Thus, it appears that the students were not randomized for testing, and the individuals performing the pulmonary function tests were not blinded with respect to the students' school and, therefore, to the exposure group. In addition, there is no indication in the report whether or not the pulmonary function measurements were adjusted for sex, age, height, and weight of the children. Because of both of these problems, the pulmonary function observations as reported in the Nogawa study may be biased seriously.

A third problem with the Nogawa study is that the exposure levels in the study were very poorly defined. Total dust fall is a poor measure of individual exposure; the investigators also did not comment on the size of the dust particles. It should also be noted that the accuracy of the EPA's calculations regarding the manganese levels in the Nogawa study have not been validated. Finally, the authors did not take into account several factors that are known to affect the health status of children; for example, parental smoking, socioeconomic status, and exposure to other pollutants emitted from the plant. The failure to take such confounding factors into account may have also affected the outcome of the study.

The Nogawa study was performed in 1970. Subsequently, dust collectors were installed in the factory, which led to a dramatic decline in the emissions of manganese (the actual

levels of manganese are not reported) (Kagamimori et al. 1973). In a follow-up study, Kagamimori et al. (1973) studied the prevalence of subjective symptoms and ventilatory functions in the same schools and in many of the same children. Both the subjective symptoms and the ventilatory function of the students of the school in the vicinity of the plant were reported to have improved in comparison to those of students of the "control school," and in comparison to results obtained in the original survey. The improvements were less marked among students of higher grades, who had also shown a greater effect on the ventilatory function during the original study.

The Kagamimori study suffered from most of the same problems as the Nogawa study. The results of the Kagamimori study were seen by its authors as providing support for the validity of the Nogawa study. However, the problems with the design, analysis, and reporting of the Nogawa study, as well as the Kagamimori study, are serious, and therefore their conclusions are not reliable. Although we do not know whether or not there are any differences in the responsiveness between children and adults, the Nogawa study stands alone in reporting respiratory health effects of manganese at levels as low as 3 to 11 $\mu g/m^3$; the results of all other studies, which have focused on adults, suggest pulmonary effects at or between one to two orders of magnitude greater exposure.

Animal Studies: A number of animal studies have been performed to explore the respiratory toxicity of manganese. Exposure to high levels of manganese appears to produce an inflammatory response and decreases the number and phagocytic activity of alveolar macrophages. If exposure to manganese is performed in conjunction with bacterial challenge, an

enhancement in the susceptibility to bacterial infections is also observed; this is believed to be a consequence of the decrease in the number and activity of alveolar macrophages.

Many of the early studies on respiratory effects of manganese used protocols in which the animals were exposed to high levels of manganese for short durations; such studies are not very helpful in understanding the effects of prolonged exposure at low levels. In several recent studies, animals have been exposed to relatively low levels of manganese (Table 6). Suzuki et al. (1978) exposed Rhesus monkeys to 700 and 3,000 $\mu g/m^3$ of MnO_2 dust for 22 hr/day, for 10 months, and reported that morphologic and inflammatory changes occurred earlier in animals exposed to higher levels of manganese. Adkins et al. (1980b) exposed CD mice for two hours to 220 to 2,650 $\mu g/m^3$ of Mn_3O_4 in conjunction with Streptococcus pyrogenes. They reported a dose-related enhancement in mortality; based on regression analysis, a 7.5 percent increase in mortality was predicted, with 95 percent confidence, at 0.38 mg Mn/m^3.

Two other studies, which employed lower levels of manganese, reported negative results. Ulrich et al. (1979a,b,c) exposed SD rats and squirrel monkeys to Mn_3O_4 particles at 0, 11.6, 112.5, and 1152 $\mu g/m^3$ for 24 hr/day for 9 months, and reported no morphologic or functional changes. Coulston and Griffin (1976) exposed Rhesus monkeys to 100 $\mu g/m^3$ of Mn_3O_4 for 24 hr/day, for 66 weeks, and reported no manganese-related effects.

Other investigators have studied the cells isolated from lung lavage fluid from animals exposed to manganese compounds. Camner et al. (1985) exposed rabbits to 1,100 and 3,900 $\mu g/m^3$ $MnCl_2$ for 6 hr/day, 5 days/week, for 4 weeks, and

reported no effects on the number or phagocytic activity of alveolar macrophages; the only significant effect in this study was an increase in the diameter of alveolar macrophages. In rabbits exposed under the same conditions, Bergham et al. (1987) reported no change in the levels of fibronectin or lysozymal activity in the lung lavage fluid.

Thus, the animal literature on the effects of low-level exposure to manganese is not very extensive. It is clear that exposure to high levels of manganese produces an inflammatory response in the lung of laboratory animals, a decrease in the number and activity of alveolar macrophages, and an increase in the susceptibility to infections; however, these responses have not been unequivocally demonstrated at the low levels of exposure that are of interest in the context of this report. Although the available information does not allow us to draw a definite conclusion regarding the lowest observable adverse effect level, the animal studies have been used by the EPA to calculate the human equivalent exposure levels (HEEL) for studies indicating no observed effect levels (NOEL), and the lowest observed adverse effect level (LOAEL) (U.S. Environmental Protection Agency 1984). After applying a correction factor of 10 to account for potentially sensitive individuals, the EPA derived a HEEL of 5 $\mu g\ Mn/m^3$ based the NOEL reported in the rat, and 8.7 $\mu g\ Mn/m^3$ based on the NOEL reported in the squirrel monkey (Ulrich et al. 1979a,b,c); the EPA also derived a HEEL of 36.5 $\mu g\ Mn/m^3$ based on the LOAEL in the Rhesus monkey (Suzuki et al. 1978).

EXPOSURE TO MANGANESE

Anticipated Exposure Levels of Manganese from Automotive Sources

Without the use of manganese fuel additives, the contribution of motor vehicle emissions to ambient manganese levels is probably very small. In the 1970s, a manganese-containing fuel additive, methylcyclopentadienyl manganese tricarbonyl (MMT) was included in the United States in some unleaded gasolines to improve octane ratings for a limited period of time. Consequently, some efforts were made to estimate and measure the increased manganese concentrations in air associated with the additive's use. Ter Haar et al. (1975) estimated that the median urban increment would be 0.05 μg Mn/m^3 if MMT was used in all vehicles and fuel concentrations of manganese were 0.125 g/gal. Pierson et al. (1978), with the use of aerosol sampling, determined manganese levels in the Allegheny and Tuscarora Tunnels of the Pennsylvania Turnpike for several one-week intervals between 1975 and 1977. (In this period, the use of MMT was at its peak; however, in 1978, the use of MMT as an additive to unleaded gasoline was terminated.) The highest average weekly level inside the tunnels was 0.13 μg Mn/m^3, and the average for the measurement periods was 0.11 μg Mn/m^3. The peak use of MMT during the study (1977) resulted in an average value of 16 mg manganese per gallon of gasoline in vehicles traveling through the tunnels; corresponding manganese-emission rates were 0.13 mg/mile. These data suggest that in locations with a heavy flow of traffic emitting MMT-derived manganese into a confined space, increased manganese levels at roadside may be discriminated from background levels. One of the important unknowns, and a possible confounding factor in roadside measurements, is the extent to which traffic resuspends road

dusts that contribute to the manganese content of the roadside aerosol. Since the use of MMT has been phased out in the United States, this report does not focus on manganese emissions from MMT added to fuel.

The use of manganese fuel additives to reduce particulate emissions has been contemplated in conjunction with ceramic particulate traps. Manganese is added to the fuel to act as a catalyst in order to burn off the particles that would accumulate on the trap, and thus regenerate the trap. Lubrizol 8220, a proprietary manganese fatty acid compound, is a likely fuel additive for such applications.

The emission rates of manganese from vehicles so equipped are expected to be considerably higher than those associated with MMT use. For urban highway driving, Volkswagen estimated that emission rates would range from an expected value of 1.38 mg Mn/mile to a worst-case value of 4 mg Mn/mile; for urban street driving, expected emissions will be 3.13 mg Mn/mile with a worst-case value of 10 mg Mn/mile (Volkswagen 1984; Wiedemann 1985). The worst-case estimates are based on the assumption that all of the manganese in the fuel stream is emitted, while the expected values reflect retention of a fraction of manganese in the engine and particulate filter (the latter is the more realistic case).

Direct measurement of the emissions of manganese is not possible because the technology is not yet implemented in the active vehicle fleet. Therefore, we have to rely on modeling calculations to estimate the worst-case and the likely ambient levels of manganese. The data obtained from such modeling calculations are necessary and important for placing the health questions in perspective of expected human exposure, and they help anticipate whether situations may

arise in which manganese concentrations achieve levels that are associated with known health effects.

Volkswagen (1984) used modeling techniques to project the emission rates into manganese concentrations at the side of freeways and within street canyons. Assuming 100 percent penetration of the trap into the automobile fleet, worst-case traffic conditions, a crossroad wind, manganese consumption of 4 mg/mile on highways and 10 mg/mile in street canyons, and using the EPA HIWAY-2 model, Volkswagen calculated the manganese concentrations indicated in Table 7. The Health Effects Institute has independently verified the results from the HIWAY-2 model. The results of HEI's analyses are in general agreement with Volkswagen's results except that, for highways, the most conservative values occur with the wind parallel to the roadway (Table 8). With a parallel wind (5 degrees to the roadway) Volkswagen's worst-case highway manganese level would be 3.60 $\mu g/m^3$ instead of 2.00 $\mu g/m^3$.

These modeling exercises produce ceiling estimates based on hypothetical situations. These estimates serve a valuable purpose in that they provide a reference for applying correction factors. Perhaps the most important correction factor is penetration of the trap and manganese technology in the diesel-vehicle fleet. The California Air Resources Board (1984) estimated that by 1990, between 2.6 percent and 6.6 percent of the vehicle fleet will have particle traps (values derived from Table 1). Using these values, one may adjust the worst-case street canyon value of 7.6 μg Mn/m^3 to between 0.2 and 0.5 μg Mn/m^3 for upper-bound emission rates of 10 mg Mn/mile, and between 0.06 and 0.16 μg Mn/m^3 for expected emission rates of 3.13 mg Mn/mile. Likewise, for highways with parallel winds, manganese values at roadsde will be between 0.09 and 0.24 $\mu g/m^3$ for upper-bound emission rates of

4 mg/mile, and between 0.03 and 0.08 $\mu g/m^3$ for expected emission rates of 1.38 mg/mile.

It seems highly unlikely, therefore, that under the conditions described, automobiles equipped with the proposed particle regenerator system will contribute more than 0.5 μg Mn/m^3 to ambient air. A number of factors, however, still require attention to provide a more complete picture of manganese emissions from these automobiles. At present there is very little information on the size distribution of manganese-containing particles in the exhaust or the species of manganese compounds that are emitted (see below). Also, the modeling performed to date does not consider the vehicle operation conditions such as acceleration and steady-state driving. If the properties of manganese emissions are similar to those of lead, then the percentage of manganese exhaust may vary with the vehicle's operating condition and will increase when vehicles accelerate from a stop or a low cruise (20 mph) to a much higher speed (60 mph). This occurs because particles can build up in the exhaust system during steady-state driving and are released during high-load accelerations. If this is the case, then the roadside levels of manganese at a section of road where vehicles accelerate may be higher than the above calculations indicate.

Characteristics of the Manganese Emissions

Lubrizol 8220 contains a manganese compound that is a carboxylate salt of naturally occurring fatty acids in a complex mixture of petroleum distillate hydrocarbons. The concentration of manganese in Lubrizol is 4.5 weight percent.

The only information on the species of manganese present in exhaust from vehicles equipped with a ceramic trap is from

a report by Fritsche (1986). In a study sponsored by Volkswagen, he analyzed the material collected on the ceramic trap and reported that manganese was present as Mn(II)-Mn(III) oxides of composition similar to Mn_3O_4. It also appeared that only 1 percent of the manganese may be present in organic form.

Fritsche was not able to analyze the material that comes out of the trap and becomes airborne because these samples were collected and supplied to him by Volkswagen on glass fiber filters, which interfered with the analysis. In addition, the report does not detail the vehicles, fuel, or driving conditions under which the samples were collected; therefore, it is not possible to tell how representative the Volkswagen samples were. Finally, the report does not contain any information on the fraction of manganese in the fuel that is emitted from the tailpipe.

Thus, very little is known about the physical and chemical characteristics of manganese emissions. Based on the Fritsche (1986) study, and information on MMT (Cooper 1984), it appears likely that the manganese emissions would mostly be in the oxide form, and would be associated with fine particulate matter.

Determination of the Inhaled Dose of Manganese

Most investigators have relied on ambient air levels as an indicator of the inhaled dose of manganese. Efforts at determining personal exposure to manganese have proved very difficult. It is desirable to estimate both the recent exposure and the long-term exposure to manganese. Irrespective of the route of exposure, fecal excretion is the dominant route of elimination of manganese. Although excretion

in urine is low, some authors have investigated the relationship between urinary manganese and recent exposure. Blood manganese levels are thought to reflect cumulative exposure over long periods or the body burden.

In a recent study, Roels et al. (1987b) studied 141 workers from a plant producing manganese oxide and salt (median airborne manganese levels: 1 mg/m^3, range 0.07 to 8.61 mg/m^3), and 104 workers from a chemical plant who served as the control group. The authors reported that on an individual basis, there was no relationship between manganese levels in the urine and the blood, and neither was correlated with the manganese levels in the air, or with the duration of exposure, for an individual. Therefore, the determination of personal dose, or the body burden, based on the levels of manganese in blood or urine does not appear to be feasible. On a group basis, however, urinary manganese was slightly, but not significantly, correlated with recent exposure, and blood manganese was correlated with integrated past exposure (Roels et al. 1987b).

The Roels et al. studies (1987a,b) appear to have been well planned and carefully executed. Their results raise questions regarding the relevance of ambient levels of manganese to human dose and health effects. It should be pointed out that other studies attempting correlations between manganese levels in body fluids and exposure have given inconsistent results (discussed in Roels et al. 1987a,b). More research is needed to establish the relationships between ambient exposure, personal dose, and health effects of manganese.

DISCUSSION AND CONCLUSIONS

In order to reduce particulate emissions from diesel-fueled vehicles, the use of ceramic particulate traps, in conjunction with a manganese fuel additive, has been viewed as promising. This report has focused on the health effects of manganese and on the anticipated public exposure to manganese emissions. The preceding discussion provides the background for the following perspective on potential health risks from inhalation of manganese in automotive exhaust.

Estimation of the Worst Case Inhaled Dose

Maximum exposure to manganese-containing exhaust is likely to occur in heavily trafficked urban street canyons. Individuals such as traffic policemen, construction workers, and street vendors, who may work in a street canyon environment, are likely to receive the greatest exposure to manganese exhaust. To estimate worst-case inhaled dose, we adopt the following assumptions:

1. These individuals are exposed for eight hours each working day to worst-case manganese levels (0.5 $\mu g/m^3$).

2. For the entire eight hours, they breathe at a rate of 15 liters per minute, which for a 70 kg person, is roughly twice resting ventilation.

3. All the inspired manganese aerosol deposits in the respiratory tract.

4. Manganese is emitted from the tailpipe as an oxide.

5. Airborne manganese from other sources is small compared to 0.5 $\mu g/m^3$.

Based on these assumptions, a total of 3.6 μg of manganese deposits in the respiratory tract each working day. At least 60 percent of the deposited manganese is swept within days to several weeks into the gastrointestinal tract, from which a negligible fraction, 3 percent, is absorbed into the blood--a total of 0.065 μg. For the purpose of worst-case considerations, assume all of the remainder, 1.4 μg, is absorbed eventually through the lung and into the circulation. Thus, for each working day's worst-case manganese-aerosol exposure of 3.6 μg, roughly 1.5 μg of manganese is absorbed over time into the circulation. Dietary intake of manganese, in most cases, ranges from 2 to 9 mg/day; with 3 percent absorption, at least 60 μg of manganese enters the portal blood daily. Therefore, under the worst-case assumptions, the contribution of manganese from automobile exhaust is not anticipated to be greater than 2.5 percent of the dietary intake. This small contribution of manganese from mobile sources is not expected to tax the homeostatic mechanisms that regulate the levels of manganese throughout the body's tissues.

Two potential high-risk groups that were identified previously include iron-deficient individuals and the very young. These groups have been studied mostly in chronic animal experiments in which dietary manganese is increased by a factor of 7 or more above normal, or manganese is intubated daily at even higher levels (Rehnberg et al. 1980; Laskey et al. 1982). While the susceptibility of these groups may be observed in such studies, the actual doses inhaled from automobile-derived, airborne manganese will remain exceedingly small compared to the normal range of dietary intake.

Potential Health Effects

Is exposure to the estimated worst-case ambient level of manganese, 0.5 $\mu g/m^3$, likely to produce neurotoxic effects? High levels of manganese produce a Parkinson-disease-like neurologic disorder. Studies on neurotoxic effects in appropriate animal models have been limited and do not provide reliable dose-response information. Most human studies suggest that neurotoxic effects occur after prolonged exposure to concentrations of manganese that are 1 mg/m^3 or greater. Saric et al. (1977) have reported adverse neurologic effects in workers exposed to 0.3 to 5 mg/m^3. However, as discussed earlier, this study suffers from several deficiencies that make its interpretation difficult. In any event, the levels of manganese expected from mobile sources (0.5 $\mu g/m^3$) will be very low as compared to the lowest level in the Saric study (300 $\mu g/m^3$). Therefore, it appears very unlikely that exposure to the levels of airborne manganese derived from automobile fuel additive as estimated in their report would produce adverse neurologic effects.

Respiratory effects of manganese include bronchitis, pneumonitis, and an increase in the susceptibility to respiratory infections. Pulmonary effects of manganese have been observed at levels that are lower than those at which neurotoxic effects have been reported. Based on the results of animal studies, the lowest, human-equivalent, no observed effect level, calculated by the U.S. Environmental Protection Agency (1984, p. 14) is 5 $\mu g\ Mn/m^3$. Studies of occupationally exposed workers show that adverse pulmonary effects of manganese follow exposure in the mg/m^3 range. However, a study by Nogawa et al. (1973) suggests that adverse respiratory effects of manganese may be produced at levels as low as 3 to 11 $\mu g/m^3$. Nogawa et al. (1973) based their

conclusion on a study of subjective symptoms and pulmonary function tests in children who attended a school near a ferromanganese plant. However, several serious problems with the Nogawa study (such as poor characterization of exposure, failure to blind observers and to randomize students, and a lack of control for the confounding factors) lead us to believe that its results are not reliable. The results of all other studies suggest that adverse respiratory effects are produced at exposure levels that are one or two orders of magnitude greater than the levels in the Nogawa study.

The worst-case estimated level of manganese from its intended use in reducing particulate emissions is 0.5 $\mu g/m^3$. As compared to the no observed effect levels from animal studies (5 μg Mn/m^3 or higher), the estimated airborne manganese levels are lower. As compared to the levels at which adverse health effects have been observed in reliable epidemiologic studies, the manganese emissions from mobile sources are expected to be much lower. Therefore, it appears that the levels of airborne manganese derived from fuel additives in trap-equipped diesel-powered automobiles are not likely to produce adverse respiratory effects in the general public.

If the objections to the Nogawa study are ignored, and its results are taken prima facie, the difference between the lowest observed adverse effect level in the Nogawa study (3 μg Mn/m^3), and the worst-case manganese level from trap-equipped vehicles (0.5 $\mu g/m^3$) is not very large. The estimated worst-case manganese level is also only 10-fold lower than the no observed effects level calculated from animal studies. Therefore, if manganese were to be used as a fuel additive at some time in the future, it would be important to review the Nogawa study in greater depth than we have

done for this analysis. As discussed earlier, it would also be crucial that the emissions of manganese be characterized in terms of their physical form and chemical species. In addition, it would be important to make an intensive effort to ensure that the assumptions made in this report regarding the ambient levels of manganese, public exposure and dose of manganese, and disposition of the inhaled manganese are all valid.

The EPA issued a decision on August 13, 1985 not to regulate manganese as a hazardous air pollutant under Section 112 of the Clean Air Act (U.S. Environmental Protection Agency 1985). However, the EPA also intends to continue to monitor research activities, "and will reinstitute assessment if warranted by the results of that research." The Health Effects Institute endorses such flexibility and stands ready to reevaluate this issue as new relevant scientific and engineering data emerge or the use of the manganese technology expands beyond currently anticipated levels.

REFERENCES:

Abrams E, Lassiter JW, Miller WJ, Neathery MW, Gentry RP, Scarth RD. 1976. Absorption as a factor in manganese homeostasis. J. Anim. Sci. 42:630-636.

Adkins B Jr, Luginbuhl GH, Gardner DE. 1980a. Acute exposure of laboratory mice to manganese oxide. Am. Ind. Hyg. Assoc. J. 41:494-500.

Adkins B Jr, Luginbuhl GH, Miller FJ, Gardner DE. 1980b. Increased pulmonary susceptibility to streptococcal infection following inhalation of manganese oxide. Environ. Res. 23:110-120.

Berghem L, Hasson M, Lundborg M, Camner P. 1987. Fibronectin concentrations in lung lavage fluid after inhalation exposure to low levels of metals. Environ Res. 43:179-185.

Brain JD, Knudson DE, Sorokin SP, Davis MA. 1976. Pulmonary distribution of particles given by intratracheal instillation or by aerosol inhalation. Environ. Res. 11:13-33.

Brain JD, Valberg PA. 1979. Deposition of aerosol in the respiratory tract. Am. Rev. Respir. Dis. 120:1325-1373.

Britton AA, Cotzias GC. 1966. Dependence of manganese turnover on intake. Am. J. Physiol. 211:203-206.

Cahill DF, Bercegeay MS, Haggerty RC, Gerding JE, Gray LE. 1980. Age-related retention and distribution of ingested Mn_3O_4 in the rat. Toxicol. Appl. Pharmacol. 53:83-91.

California Air Resources Board, September 20, 1984. Memorandum: Modeling analysis of potential impacts of manganese as a diesel fuel additive. Sacramento, CA.

Camner P, Curstedt T, Jarastrand C, Johannsson A, Robertson B, Wiernik A. 1985. Rabbit lung after inhalation of manganese chloride: A comparision with the effects of chlorides of nickel, cadmium, cobalt and copper. Environ. Res. 38: 301-309.

Cooper WC. 1984. The health implications of increased manganese in the environment resulting from the combustion of fuel additives: A review of the literature. J. Toxicol. Environ. Health 14:23-46.

Cotzias GC, Horiuchi K, Fuenzalida S, Mena I. Chronic manganese poisoning: Clearance of tissue manganese

concentrations with persistence of the neurological picture. Neurology 18:376-382, 1968.

Coulston F, Griffin T. 1976. Inhalation toxicology of airborne particulate manganese in rhesus monkeys. Institute of Comparative and Human Toxicology, International Center of Environmental Safety, Albany Medical College, Holloman Air Force Base, NM. EPA-68-02-0710. (Also EPA-600/1-77-026, May 1977.)

Drown DB, Oberg SG, Sharma RP. Pulmonary clearance of soluble and insoluble forms of manganese. J. Toxicol. Environ. Health 17:201-212, 1986.

Fraunhofer-Institut fur Toxikologie und Aerosolforschung Institutsteil, Hannover/Munster. February 1984. Evaluation of health effects associated with the diesel trap oxidizer regeneration: A literature search. Under contract with Volkswagenwerk AG.

Fritsche U. 1986. Investigations for the determination of the chemical compound of the manganese, which is used in a catalysing additive and can be emitted by diesel engines. Report of the Fraunhoffer Institute for Environmental Chemistry and Ecotoxicology, Hanover/Munster.

Greenberg DM, Campbell WW. Studies in mineral metabolism with the aid of induced radioactive isotopes. IV. Manganese. Proc. Natl. Acad. Sci. USA 26:448-452, 1940.

Greenberg DM, Copp DH, Cuthbertson EM. Studies in mineral metabolism with the aid of artificial radioactive isotopes. VII. The distribution and excretion, particularly by way of the bile of iron, cobalt, and manganese. J. Biol. Chem. 147:749-756, 1943.

Kagamimori S, Makino T, Hiramaru Y, Kawano S, Kato T, Nogawa K, Kobayashi E, Sakamoto N, Fukushima M, Ishizaki A, Tanagawa K, Azami S. Studies concerning the effects of the respiratory organs of atmospheric pollution caused by dusts consisting chiefly of manganese. (Second report) Concerning the changes in the effects on the human organism when the environment is improved. Nihon Koshu Eiser Gakkai Shi (J. Japan Soc. Pub. Health) 20:413-420, 1973.

Klaasen CD. Biliary excretion of manganese in rats, rabbits, and dogs. Toxicol. Appl. Pharmacol. 29:458-468, 1974.

Kostial K, Kello D, Jugo S, Rabar I, Maljkovic T. Influence of age on metal metabolism and toxicity. Environ. Health Perspect. 25:81-86, 1978.

Laskey JW, Rehnberg GL, Hein JF, Carter SD. Effects of chronic manganese (Mn_3O_4) exposure on selected reproductive parameters in rats. J. Toxicol. Environ. Health 9:677-687, 1982.

Lundborg M, Lind B, Camner P. Ability of rabbit alveolar macrophages to dissolve metals. Exp. Lung Res. 7:11-22, 1984.

Mahoney JP, Small WJ. Studies on manganese. III. The biological half-life of radiomanganese in man and factors which affect this half-life. J. Clin. Invest. 47:643-653, 1968.

Mena I, Horiuchi K, Burke K, Cotzias GC. Chronic manganese poisoning: Individual susceptibility and absorption of iron. Neurology 19:1000-1006, 1969.

Mena I, Horiuchi K, Lopez G. Factors enhancing entrance of manganese into the brain: Iron deficiency and age (abs) J. Nuc. Med. 15:516, 1974.

Mena I, Marin O, Fuenzalida S, Cotzias GC. Chronic manganese poisoning: Clinical picture and manganese turnover. Neurology 17: 128-136 1967.

Mouri T. Experimental studies on the inhalation of manganese dust. Shikoku Acta Med. 28:118-129, 1973.

National Research Council, Committee on Biologic Effects of Atmospheric Pollutants, Division of Medical Sciences. Manganese. National Academy of Sciences, Washington, DC, 1973.

Nogawa K, Kobayashi E, Sakamoto M, Fukushima N, Ishizaki A, Makino N, Kagamimori S, Hiramaru Y, Kawano S, Kato T, Kanekawa KJ, Shozo. Studies of the effects on the respiratory organs of air pollution consisting of dusts composed mainly of manganese. (First Report) Effects on the respiratory organs of junior high school students. Nippon Koshu Eisei Zasshi (Jap. J. Public Health) 20:315-325, 1973.

Pierson WR, McKee DE, Brachaczek WW, Butler JW. Methylcyclopentadienyl manganese tricarbonyl: Effect on manganese emissions from vehicles on the road. J. Air Pollut. Control Assoc. 28:692-693, 1978.

Pollack S, George JN, Reba RC, Kaufman RM, Crosby WH. The absorption of nonferrous metals in iron deficiency. J. Clin. Invest. 44:1470-1473, 1965.

Raabe OG. Deposition and clearance of inhaled aerosols. In: Mechanisms in Respiratory Toxicology (Witschi H, Nettesheim P, eds.) CRC Press, Inc., Boca Raton, FL, 1982.

Rehnberg GL, Hein JF, Carter SD, Laskey JW. Chronic manganese oxide administration to preweanling rats: Manganese accumulation and distribution. J. Toxicol. Environ. Health 6:217-226, 1980.

Rehnberg GL, Hein JF, Carter SD, Linko RS, Laskey JW. Chronic ingestion of Mn_3O_4 by young rats: Tissue accumulation, distribution, and depletion. J. Toxicol. Environ. Health 7:263-272, 1981.

Rehnberg GL, Hein JF, Carter SD, Linko RS, Laskey JW. Chronic ingestion of Mn_3O_4 by rats: Tissue accumulation and distribution of manganese in two generations. J. Toxicol. Environ. Health 9:175-188, 1982.

Roels H, Lauwerys R, Buchet J-P, Genet P, Sarhan M J, Hanotiau I, de Fays M, Bernard A, Stanescu D. Epidemiological survey among workers exposed to manganese: Effects on lung, central nervous system, and some biological indices. Am. J. Ind. Med. 11:307-327, 1987a.

Roels H, Lauwerys R, Genet P, Sarhan MJ, de Fays M, Hanotiau I, Buchet J-P. Relationship between external and internal parameters of exposure to manganese in workers from a manganese oxide and salt producing plant. Am. J. Ind. Med. 11:297-305, 1987b.

Saric M, Markicevic A, Hrustic O. Occupational exposure to manganese. Br. J. Ind. Med. 34: 114-118, 1977.

Stuart BO. Deposition and clearance of inhaled particles. Environ. Health Perspect. 55:369-390, 1984.

Suzuki Y. Studies on excessive oral intake of manganese. II. Minimum dose for manganese accumulation in mouse organ. Shikoku Acta Med. 30:32-45, 1974.

Suzuki Y, Fuji N, Yano H, Ohkita T, Ichikawa A, Nishimaya K. Effects of the inhalation of manganese dioxide dust on monkey lungs. Tokushima J. Exp. Med. 25:119-125, 1978.

Ter Haar GL, Griffing ME, Brandt M, Oberding DG, Kapron M. Methylcyclopentadienyl manganese tricarbonyl as an antiknock: Composition and fate of manganese exhaust products. J. Air Pollut. Control Assoc. 25:858-860, 1975.

Ulrich CE, Rinehart W, Busey W. Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol. I. Intro-

duction, experimental design and aerosol generation methods. Am. Ind. Hyg. Assoc. J. 40:238-244, 1979a.

Ulrich CE, Rinehart W, Busey W, Dorato MA. Evaluation of the chronic inhalation toxicity of a manganese oxide aerosol. II. Clinical observations, hematology, clincial chemistry and histopathology. Am. Ind. Hyg. Assoc. J. 40:322-329, 1979b.

Ulrich CE, Rinehart W, Brandt M. Evaluation of the cronic inhalation toxicity of a manganese oxide aerosol. III. Pulmonary function, electromyograms, limb tremor, and tissue manganese data. Am. Ind. Hyg. Assoc. J. 40:349-353, 1979c.

U.S. Environmental Protection Agency. August 1984. Health Assessment Document for Manganese. Environmental Criteria and Assessment Office. Final Report. EPA-60018-83-013F.

U.S. Environmental Protection Agency. August 13, 1985. Decision not to regulate manganese concentrations as hazardous air pollutant under Section 112 of Air Act. Federal Register 50:32627-32628.

Volkswagen. March 13, 1984. Manganese concentrations in air resulting from the possible use of manganese compounds as a diesel fuel additive and health effect aspects of manganese. Wolfsburg, West Germany.

Wiedemann B, Neumann KH. Vehicular experience with additives for regeneration of ceramic diesel filters. Volkswagenwerk AG, Wolfsburg, West Germany, SAE Technical Paper Series No. 850017, Warrendale, PA, 1985.

TABLE 1

Ambient Manganese Concentrations by State from EPA's SAROAD Data

State	Number of Samples	1980-1982 SAROAD Data (ug/m^3) (24 hour averages) range	mean	Site Characteristics*
Alabama	164	0-0.360	0.065	urban/suburban - Birmingham
	30	0.005-0.046	0.028	urban, rural
Arizona	1214	0-0.220	0.059	urban, rural
	64	0.003-0.070	0.025	rural, urban
	38	0-0.011	0.003	national park
Arkansas	27	0.002-0.038	0.009	national forest
	27	0.009-0.037	0.019	urban/suburban
California	65	0-0.080	0.028	rural/suburban, national forest
	97	0.004-0.060	0.024	urban, national forest/desert
	104	0-0.050	0.020	urban, rural
	78	0-0.070	0.025	urban - Los Angeles, San Francisco
Colorado	290	0-0.170	0.057	urban, rural
	79	0-0.060	0.028	national forest, rural, urban
	54	0-0.180	0.077	rural, national forest
	57	0-0.030	0.005	national forest
Connecticut	25	0.003-0.026	0.015	urban, rural
Delaware	21	0.002-0.050	0.018	urban/suburban
DC	24	0.010-0.032	0.019	urban
Florida	110	0-0.030	0.007	Everglades/ national park, urban
	206	0-0.032	0.011	urban, rural
Georgia	49	0-0.107	0.025	urban/suburban
	55	0-0.051	0.016	military reservation

TABLE 1 (continued)

Ambient Manganese Concentrations by State from EPA's SAROAD Data

State	Number of Samples	1980-1982 SAROAD Data (ug/m^3) (24 hour averages) range	mean	Site Characteristics*
Hawaii	107	0-0.024	0.006	urban/suburban, national park
Indiana	77	0.004-0.103	0.019	urban
	164	0-0.045	0.024	rural, urban
	58	0.009-0.759	0.151	rural, urban - Gary
Iowa	142	0-0.130	0.034	rural, urban
Kansas	84	0.008-0.097	0.037	urban, rural - Kansas City - Topeka
Kentucky	66	0.004-0.299	0.042	suburban, rural
	41	0.009-0.133	0.047	rural
	354	0-0.182	0.026	urban
Louisiana	131	0-0.039	0.017	urban
	70	0.004-0.081	0.029	suburban
	36	0-0.021	0.009	rural
Maryland	21	0.018-0.261	0.107	urban - Baltimore
	25	0.010-0.220	0.069	urban, rural - Baltimore Co.
Massachusetts	42	0-0.029	0.010	urban
	28	0.006-0.032	0.017	rural
Michigan	35	0.004-0.050	0.017	rural
	46	0-0.140	0.036	urban/suburban - Flint
Minnesota	25	0-0.050	0.022	urban/suburban
Mississippi	25	0.007-0.058	0.023	urban, rural

TABLE 1 (continued)

Ambient Manganese Concentrations by State from EPA's SAROAD Data

State	Number of Samples	1980-1982 SAROAD Data (ug/m^3) (24 hour averages) range	mean	Site Characteristics*
Montana	98	0-0.190	0.026	rural, urban
	78	0-0.080	0.029	national forest
	146	0-0.350	0.065	national forest, suburban/ military reservation
Nebraska	40	0.005-0.073	0.029	urban/suburban
Nevada	46	0.004-0.041	0.019	national forest, urban - Las Vegas
	114	0-0.066	0.015	forest, mountains
New Jersey	189	0-0.129	0.024	urban/suburban
New Mexico	43	0.007-0.069	0.031	urban
New York	45	0.002-0.079	0.023	rural/suburban, state park
	314	0-0.580	0.029	urban/suburban
North Carolina	48	0-0.0284	0.004	national forest
	133	0-0.071	0.015	urban, rural
Ohio	34	0.018-0.183	0.073	urban - Cleveland
	46	0-0.050	0.020	urban - Toledo, rural
	291	0-0.170	0.036	urban/suburban
	23	0.003-0.173	0.045	suburban, rural
Oklahoma	39	0.005-0.061	0.022	rural, suburban
	41	0.005-0.035	0.017	urban/suburban
Pennsylvania	58	0.010-0.960	0.120	urban - Philadelphia
	22	0.004-0.040	0.019	urban, rural
	65	0.005-0.184	0.049	rural, suburban

TABLE 1 (continued)

Ambient Manganese Concentrations by State from EPA's SAROAD Data

State	Number of Samples	1980-1982 SAROAD Data (ug/m^3) (24 hour averages) range	mean	Site Characteristics*
South Carolina	132	0-0.039	0.013	rural, urban
South Dakota	30	0-0.010	0.005	national forest
Tennessee	111	0.003-0.070	0.028	urban
	72	0.005-0.290	0.051	national forest, rural - Sullivan County
	115	0.002-0.190	0.052	rural, urban
Texas	1519	0-0.457	0.021	urban/suburban
	339	0-0.072	0.015	rural
	636	0-0.343	0.023	suburban
	805	0-0.397	0.022	rural, urban
Virginia	48	0-0.027	0.006	national forest
	45	0-0.026	0.011	urban, rural
	21	0-0.014	0.007	urban - Danville
	130	0-0.050	0.017	urban/suburban
Washington	207	0-0.129	0.027	national forest, rural, urban
West Virginia	22	0.010-0.090	0.036	rural, urban
Wisconsin	49	0-0.020	0.005	rural
	94	0.004-0.255	0.044	urban/suburban - Milwaukee
	80	0-0.140	0.021	rural, urban
Wyoming	24	0-0.010	0.002	national forest

* Site characteristics are listed in order of predominance.

Table 2: Examples of Levels of Occupational Exposure to Airborne Manganese[a]

Operation	Range of averages[b] (μg Mn/m³)	Range of peak levels[b] (μg Mn/m³)	References
Ore crushing mill	10,400–173,000	–	Flinn et al. (1940)
Ore crushing	62,500–250,000	–	Ansola et al. (1944)
Permanganate manufacture	300–250,000	–	Lloyd Davies (1947)
Mining, mine #1	187,000–926,000	–	Rodier (1955)
Mining, mine #2	65,000–814,000	–	Rodier (1955)
Mining, 1954	500–16,300	–	Schuler et al. (1957)
Mining, 1955	1,800–46,000	–	Schuler et al. (1957)
Ferromanganese production	2,300–4,700[c]	–	Whitlock et al. (1966)
Mn ore processing	5,030–11,100	5,250–31,500	Tanaka and Lieben (1969)
Ferromanganese production	1,600–8,600	4,430–20,130	Tanaka and Lieben (1969)
Dry battery manufacture	6,800–42,200	–	Emara et al. (1971)
Ferromanganese production			
Old preparation plant	27,000–1,122,000	52,000–1,750,000	Smyth et al. (1973)
Blast furnace and pig casting[d]	120–13,300	1,900–206,000	Smyth et al. (1973)
Mn processing	2,100–12,900	5,000–61,500	Smyth et al. (1973)
Ferroalloy production	301–20,440	–	Šarić et al. (1977)
Ferromanganese production (after controls)			
Blast furnace cast house[d]	230–820	1,100–22,600	Ruhf (1978)
Pig casting	390–620	3,960–5,200	Ruhf (1978)
Mn processing	390–2,260	1,000–24,300	Ruhf (1978)

[a] All studies prior to 1978 were associated with evidences of manganese toxicity in some individuals.
[b] Methods of sample collection differ, i.e., thermal precipitation, electrostatic precipitation, millipore filter sampling.
[c] Values later found to be too low.
[d] F = fume.

from: Cooper, 1984.

Table 3: *Guidelines and Standards for Manganese in the Workplace*[a]

Source	Applicable dates	Guideline or standard
ACGIH TLV	1946–1959	6000 $\mu g/m^3$ (TWA)
	1960–1962	5000 $\mu g/m^3$ (TWA)
	1963–	5000 $\mu g/m^3$ (Ceiling value)
	1978–	1000 $\mu g/m^3$ (TWA for Mn tetroxide)
	1979–	1000 $\mu g/m^3$ (TWA for Mn fume)
		3000 $\mu g/m^3$ (STEL for Mn fume)
OSHA	1972–	5000 $\mu g/m^3$ (Ceiling value)
WHO	1980–	300 $\mu g/m^3$ (TWA)

[a]Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; OSHA, Occupational Safety and Health Administration; WHO, World Health Organization; TLV, threshold limit value; TWA, time-weighted average; STEL, short-term exposure level.

from: Cooper, 1984.

Table 2

Ambient Manganese Concentrations by State from EPA's SAROAD Data

State	Number of Samples	1980-1982 SAROAD Data (ug/m^3) (24 hour averages) range	mean	Site Characteristics*
Alabama	164	0-0.360	0.065	urban/suburban - Birmingham
	30	0.005-0.046	0.028	urban, rural
Arizona	1214	0-0.220	0.059	urban, rural
	64	0.003-0.070	0.025	rural, urban
	38	0-0.011	0.003	national park
Arkansas	27	0.002-0.038	0.009	national forest
	27	0.009-0.037	0.019	urban/suburban
California	65	0-0.080	0.028	rural/suburban, national forest
	97	0.004-0.060	0.024	urban, national forest/desert
	104	0-0.050	0.020	urban, rural
	78	0-0.070	0.025	urban - Los Angeles, San Francisco
Colorado	290	0-0.170	0.057	urban, rural
	79	0-0.060	0.028	national forest, rural, urban
	54	0-0.180	0.077	rural, national forest
	57	0-0.030	0.005	national forest
Connecticut	25	0.003-0.026	0.015	urban, rural
Delaware	21	0.002-0.050	0.018	urban/suburban
DC	24	0.010-0.032	0.019	urban
Florida	110	0-0.030	0.007	Everglades/ national park, urban
	206	0-0.032	0.011	urban, rural
Georgia	49	0-0.107	0.025	urban/suburban
	55	0-0.051	0.016	military reservation

Table 2 (continued)

Ambient Manganese Concentrations by State from EPA's SAROAD Data

State	Number of Samples	1980-1982 SAROAD Data (ug/m^3) (24 hour averages) range	mean	Site Characteristics*
Hawaii	107	0-0.024	0.006	urban/suburban, national park
Indiana	77	0.004-0.103	0.019	urban
	164	0-0.045	0.024	rural, urban
	58	0.009-0.759	0.151	rural, urban - Gary
Iowa	142	0-0.130	0.034	rural, urban
Kansas	84	0.008-0.097	0.037	urban, rural - Kansas City - Topeka
Kentucky	66	0.004-0.299	0.042	suburban, rural
	41	0.009-0.133	0.047	rural
	354	0-0.182	0.026	urban
Louisiana	131	0-0.039	0.017	urban
	70	0.004-0.081	0.029	suburban
	36	0-0.021	0.009	rural
Maryland	21	0.018-0.261	0.107	urban - Baltimore
	25	0.010-0.220	0.069	urban, rural - Baltimore Co.
Massachusetts	42	0-0.029	0.010	urban
	28	0.006-0.032	0.017	rural
Michigan	35	0.004-0.050	0.017	rural
	46	0-0.140	0.036	urban/suburban - Flint
Minnesota	25	0-0.050	0.022	urban/suburban
Mississippi	25	0.007-0.058	0.023	urban, rural

Table 2 (continued)

Ambient Manganese Concentrations by State from EPA's SAROAD Data

State	Number of Samples	1980-1982 SAROAD Data (ug/m^3) (24 hour averages) range	mean	Site Characteristics*
Montana	98	0-0.190	0.026	rural, urban
	78	0-0.080	0.029	national forest
	146	0-0.350	0.065	national forest, suburban/ military reservation
Nebraska	40	0.005-0.073	0.029	urban/suburban
Nevada	46	0.004-0.041	0.019	national forest, urban - Las Vegas
	114	0-0.066	0.015	forest, mountains
New Jersey	189	0-0.129	0.024	urban/suburban
New Mexico	43	0.007-0.069	0.031	urban
New York	45	0.002-0.079	0.023	rural/suburban, state park
	314	0-0.580	0.029	urban/suburban
North Carolina	48	0-0.0284	0.004	national forest
	133	0-0.071	0.015	urban, rural
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	46	0-0.050	0.020	urban - Toledo, rural
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	23	0.003-0.173	0.045	suburban, rural
Oklahoma	39	0.005-0.061	0.022	rural, suburban
	41	0.005-0.035	0.017	urban/suburban
Pennsylvania	58	0.010-0.960	0.120	urban - Philadelphia
	22	0.004-0.040	0.019	urban, rural
	65	0.005-0.184	0.049	rural, suburban

Table 2 (continued)

Ambient Manganese Concentrations by State from EPA's SAROAD Data

State	Number of Samples	1980-1982 SAROAD Data (ug/m^3) (24 hour averages) range	mean	Site Characteristics*
South Carolina	132	0-0.039	0.013	rural, urban
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	72	0.005-0.290	0.051	national forest, rural - Sullivan County
	115	0.002-0.190	0.052	rural, urban
Texas	1519	0-0.457	0.021	urban/suburban
	339	0-0.072	0.015	rural
	636	0-0.343	0.023	suburban
	805	0-0.397	0.022	rural, urban
Virginia	48	0-0.027	0.006	national forest
	45	0-0.026	0.011	urban, rural
	21	0-0.014	0.007	urban - Danville
	130	0-0.050	0.017	urban/suburban
Washington	207	0-0.129	0.027	national forest, rural, urban
West Virginia	22	0.010-0.090	0.036	rural, urban
Wisconsin	49	0-0.020	0.005	rural
	94	0.004-0.255	0.044	urban/suburban - Milwaukee
	80	0-0.140	0.021	rural, urban
Wyoming	24	0-0.010	0.002	national forest

* Site characteristics are listed in order of predominance.

Table 3

Examples of Levels of Occupational Exposure to Airborne Manganese[a]

Operation	Range of averages[b] (μg Mn/m³)	Range of peak levels[b] (μg Mn/m³)	References
Ore crushing mill	10,400–173,000	–	Flinn et al. (1940)
Ore crushing	62,500–250,000	–	Ansola et al. (1944)
Permanganate manufacture	300–250,000	–	Lloyd Davies (1947)
Mining, mine #1	187,000–926,000	–	Rodier (1955)
Mining, mine #2	65,000–814,000	–	Rodier (1955)
Mining, 1954	500–16,300	–	Schuler et al. (1957)
Mining, 1955	1,800–46,000	–	Schuler et al. (1957)
Ferromanganese production	2,300–4,700[c]	–	Whitlock et al. (1966)
Mn ore processing	5,030–11,100	5,250–31,500	Tanaka and Lieben (1969)
Ferromanganese production	1,600–8,600	4,430–20,130	Tanaka and Lieben (1969)
Dry battery manufacture	6,800–42,200	–	Emara et al. (1971)
Ferromanganese production			
Old preparation plant	27,000–1,122,000	52,000–1,750,000	Smyth et al. (1973)
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Mn processing	2,100–12,900	5,000–61,500	Smyth et al. (1973)
Ferroalloy production	301–20,440	–	Šarić et al. (1977)
Ferromanganese production (after controls)			
Blast furnace cast house[d]	230–820	1,100–22,600	Ruhf (1978)
Pig casting	390–620	3,960–5,200	Ruhf (1978)
Mn processing	390–2,260	1,000–24,300	Ruhf (1978)

[a] All studies prior to 1978 were associated with evidences of manganese toxicity in some individuals.
[b] Methods of sample collection differ, i.e., thermal precipitation, electrostatic precipitation, millipore filter sampling.
[c] Values later found to be too low.
[d] F = fume.

from Cooper, 1984

Table 4

Guidelines and Standards for Manganese in the Workplace[a]

Source	Applicable dates	Guideline or standard
ACGIH TLV	1946-1959	6000 μg/m³ (TWA)
	1960-1962	5000 μg/m³ (TWA)
	1963-	5000 μg/m³ (Ceiling value)
	1978-	1000 μg/m³ (TWA for Mn tetroxide)
	1979-	1000 μg/m³ (TWA for Mn fume)
		3000 μg/m³ (STEL for Mn fume)
OSHA	1972-	5000 μg/m³ (Ceiling value)
WHO	1980-	300 μg/m³ (TWA)

[a]Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; OSHA, Occupational Safety and Health Administration; WHO, World Health Organization; TLV, threshold limit value; TWA, time-weighted average; STEL, short-term exposure level.

from Cooper, 1984

Table 5

RESULTS OF VOLKSWAGEN MODELING

Roadway	Emission rates (mg Mn/mi)	Roadside concentration ($ug\ Mn/m^3$)
Highway	4.00	1.98
	1.38	0.64
Street Canyon	10.00	7.60
	3.13	2.20

Table 6

ESTIMATED AMBIENT Mn CONCENTRATIONS
DOWNWIND OF A HIGHWAY
(100% penetration)

Wind Direction to Roadway	Emission Rates (mg Mn/mile)	Estimated Concentrations 4m Dnwnd ($ug\ Mn/m^3$)	100m Dnwnd ($ug\ Mn/m^3$)
Volkswagen Analysis			
90°	4.00	1.98	0.84
90°	1.38	0.64	0.22
HEI Analysis			
90°	4.00	2.00	0.80
90°	1.38	0.68	0.29
45°	4.00	2.50	1.20
45°	1.38	0.87	0.39
5°	4.00	3.60	2.50
5°	1.38	1.14	0.87

ATTACHMENT C

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

ANN ARBOR, MICHIGAN 48105

OFFICE OF
AIR AND RADIATION

AUG 1 1 1986

MEMORANDUM

SUBJECT: HEI's Role in Assessing the Health Effects of Unregulated Pollutants: (1) EPA's Request for an Evaluation of Manganese and (2) the Meaning of "Conclusive Data" in Maxwell letter of March 24, 1986

FROM: Charles L. Gray, Jr.
Director
Emission Control Technology Division
United States Environmental Protection Agency

Thomas P. Grumbly
Executive Director
Health Effects Institute

Robert Maxwell
Director
Certification Division
United States Environmental Protection Agency

TO: The Record

This memorandum summarizes, and provides background information, concerning a telephone discussion on June 5, 1986 among the following participants.

Thomas P. Grumbly, Executive Director
Health Effects Institute

Dr. Ken Sexton, Director
Scientific Review and Evaluation
Health Effects Institute

Dr. Robert Kavet, Senior Staff Scientist
Health Effects Institute

Mr. Charles Gray, Director
Emission Control Technology Division
Office of Mobile Sources
Environmental Protection Agency

Mr. Phil Lorang, Chief,
Technical Support Staff
Emission Control Technology Division
Office of Mobile Sources
Environmental Protection Agency

Mr. Robert Maxwell, Director
Certification Division, Office of Mobile Sources
Environmental Protection Agency

Dr. Joseph Somers,
Office of Mobile Sources
Environmental Protection Agency

Ms. Penny Carey
Office of Mobile Sources
Environmental Protection Agency

Mr. Matthew Wagner
Office of Mobile Sources
Environmental Protection Agency

The discussion dealt with HEI's response to Volkswagen's request of June 1984 on manganese, the general role of HEI in the unregulated pollutant evaluation process, and the meaning of "conclusive data" as expressed in Mr. Robert Maxwell's letter of March 24, 1986 to Volkswagen and more general guidance provided to manufacturers by Mr. Maxwell in a letter of April 2, 1986. The telephone call was initiated in response to a prior request by Mr. Grumbly to Mr. Richard Wilson, Director of the Office of Mobile Sources.

I. Introduction: The Statutory Framework

Section 202 (a)(4) of the Clean Air Act, 42 U.S.C. 7521 (a)(4) 1983 states:

(4) (A) Effective with respect to vehicles and engines manufactured after model year 1978, no emission control device, system, or element of design shall be used in a new motor vehicle or a new motor vehicle engine for purposes of complying with standards prescribed under this subsection if such device, system, or element of design would cause or contribute to an unreasonable risk to public health, welfare, or safety in the operation or function.

(B) In determining whether an unreasonable risk exists under subparagraph A the Administrator (of EPA) should consider among other factors:

(i) whether and to what extent the use of any device, system or element of design causes, increases, reduces or eliminates emissions of any unregulated pollutant;

(ii) available methods for reducing or eliminating any risk to public health, welfare or safety which may be associated with the use of such device, system or element of design and;

(iii) the availability of other devices, systems or elements of design which may be used to conform to the standards prescribed under this subsection without causing or contributing to such an unreasonable risk. The Administrator shall include in the consideration required by this paragraph all relevant information developed pursuant to Section 7458 of this title. [Section 7458 which codifies Section 214 requires that the Administrator conduct a study and analysis of particulate emissions of motor vehicles covered by 202(a)(4), which characterizes and quantifies such emissions and analyzes the relationship of such emissions to fuels and fuel additives used.]

A companion statute, Section 206(a)(3), 42 USC 7525 (A)(3)(1983) states:

"3(A) a certificate of conformity may be issued under this section only if the Administrator determines the manufacturer. . . . has established to the satisfaction of the Administrator that any emission control device, system, or element of design installed on, or incorporated in, such vehicle or engine, conforms to the applicable requirements of Section 7521 (a) (4) of this title.

(B) the Admistrator may conduct such tests and may require the manufacturer. . . to conduct such tests and provide such information as is necessary to carry out subparagraph A of this paragraph."

Section 206 (b), 42 USC 7525 (b) (1983), which governs the testing procedures and judicial review of certification decisions by the Administrator under this statute, provides that the Administrator is authorized to direct manufacturers to conduct tests to determine whether vehicles do conform to the regulations, and that manufacturers may file a petition with the appropriate United States Court of Appeals for judicial review of such determination. The court shall review this order in accordance with the "substantial evidence" standard of the Administrative Procedure Act. See 5 USC 706 (1977)

II. The Role of the Health Effects Institute

The Health Effects Institute was created in part to provide a mechanism for satisfying the statutory health testing obligations under section 202(a)(4). The Health Effects Institute functions to organize, fund, conduct, and evaluate research on the health effects of motor vehicle emissions. The EPA has stated that it would fully expect the Institute to become the primary mechanism by which participating motor vehicle manufacturers discharge their health testing responsibilities under 202 (a)(4) in a memorandum to the Motor Vehicle Manufacturers from Joseph A. Cannon, Assistant Administrator for Air and Radiation, and Bernard Goldstein, Assistant Administrator for Research and Development, EPA, March 20, 1984 (hereinafter the Cannon/Goldstein memorandum. Attached as Appendix A). In the Cannon/Goldstein memorandum, EPA further stated: "the EPA position on the Institute . . . will remain unchanged providing each manufacturer continues to identify in an annual written needs submission to (HEI) that health effects research which the manufacturer deems most important."

III. The HEI Manganese Report and the Maxwell Letter

Relying on the EPA's statement in the Cannon/Goldstein memorandum, Volkswagen of America, Inc. (VW) requested in June 1984 that HEI undertake an evaluation of potential health issues related to emissions from diesel automobiles using manganese-containing fuel additives for particle trap regeneration. By permitting regeneration to occur at exhaust temperatures which are reached naturally in normal operation, the manganese additive avoids the need for more expensive or otherwise less attractive regeneration approaches. Therefore within the context of the VW system, the manganese additive in question is essential to the control function of the trap and lowers emissions to levels that comply with Federal and California state environmental statutes. Any such emissions control device must meet the requirements of section 202(a)(4), that is, it must not pose an "unreasonable risk" in operation.

To fulfill its role in helping to implement 202(a)(4), HEI conducted an evaluation of manganese through its Health Research Committee. In September 1984, the Committee met, discussed the VW request and received a preliminary briefing on the toxicology of manganese. The Committee agreed to accept the request by VW and it decided that further analysis was necessary to determine whether tail pipe emissions of manganese are a public health problem, and whether HEI should sponsor research in this area. HEI subsequently commissioned Roth Associates (Dr. Neil Roth, Principal Investigator) to conduct an in-depth review of the relevant literature and studies on manganese. This review included actual replication of VW

modeling predictions of potential manganese exposure levels from use of the manganese additive and additional modeling of other emissions scenarios not analyzed by VW, plus analysis of the health effects literature. The Committee evaluated all of this information in June 1985, and conducted a final review in September 1985.

In a letter report to VW dated October 7, 1985 (hereinafter "HEI Report", HEI summarized its evaluation:

> "The evaluation first places projected Mn emissions in the context of ambient Mn levels across the United States, and then examines the health literature on Mn to establish whether the expected incremental levels of airborne Mn from regenerator-equipped automobiles are of health-related concern. Finally, we identify a number of areas in which our knowledge concerning exposure and potential effects can be improved."
>
> "To summarize our findings, increased air concentrations of Mn resulting from the use of VW's particle trap will not, under any realistic scenario, reach the lowest concentrations that have been reported in the literature to be associated with adverse chronic health effects. Despite this conclusion, certain gaps remain in our knowledge of Mn emissions and effects. These gaps primarily involve the particle size distribution and chemical species . . . in which Mn is emitted and how they might affect toxicity. The gaps in emissions characterization are best dealt with by the manufacturers directly as more experience is obtained." (HEI report, pages 2-3)

VW submitted the HEI report to the EPA in compliance with its obligations under section 202(a)(4). In response, in a letter dated March 24, 1986 (hereinafter the "Maxwell letter" in Appendix B), Robert Maxwell, Director of the Certification Division, Office of Mobile Sources, EPA, stated to VW that although VW's submission of the HEI report had "in part" met the requirements of section 202(a)(4), VW had not completed adequately the necessary submission to address the issue of unreasonable risk. The Maxwell letter asked VW to submit a detailed time schedule for providing the information on particle composition and size distribution that the HEI report noted (at p.8) was needed to "reinforce the conclusion that no health effects are expected" at the low ambient levels likely to result from its proposed use.

During the June 5, 1986 conference call, EPA staff members raised several questions about possible ambiguities in HEI's letter to Volkwagen. Taken together, these ambiguities raised doubts among EPA staff about the health effects research base for manganese. Mr. Grumbly indicated that the HEI staff had

already performed further analyses of the one Japanese study that seemed to have been conducted at exposures that approximated those thought to be of potential health concern. They had concluded that this study was quite unreliable and was probably not even a measure of manganese.

Mr. Grumbly and the HEI staff agreed with an EPA request to submit another letter on this issue and to be as unambiguious as possible in assessing the health effects data base. As part of this effort, the HEI Research Committee had asked the staff to develop an updated paper based upon the new information. Mr. Grumbly also stressed that Volkswagen still had responsibility for characterizing emissions, and that any new emissions characterization data would be carefully analyzed so that EPA had the most complete information base possible.

With respect to HEI's general role in the review of new technologies requiring certification under section 202(a)(4), EPA reiterated that it was looking to HEI to play the primary health effects research role, and to provide the Agency with HEI's views about the adequacy of the existing data base concerning new technology. HEI and EPA understand and agree that only the Agency and the manufacturers can perform the actual certification required by the standard of 202(a)(4). HEI and EPA also agreed that HEI should provide the most complete evaluation of existing evidence reasonably possible, and should provide the manufacturer with the clearest possible interpretation of that evidence, consistent with the underlying uncertainties in the scientific data base. HEI will not normally engage in quantitative risk assessment, but it will evaluate and array the available data so that EPA and the manufacturer(s) can undertake such an assessment, if the data are sufficient to warrant the effort.

IV. The Problem of "Conclusive Evidence" or "Conclusive Data"

Although it appears from the Maxwell letter that EPA will be satisfied if Volkswagen produces the information on particle composition and size distribution requested specifically, the text of the Maxwell letter went further, and HEI was concerned that its tenor could potentially create problems for HEI's role as spelled out in the Cannon/Goldstein memorandum. The letter states that section 202(a)(4) requires the manufacturer to present "conclusive evidence" or "conclusive data" that an emission control system will not cause or in any way contribute to an unreasonable risk. Both HEI and EPA agreed that "conclusive evidence" or "conclusive data" requires further explanation.

V. Summary of Positions

EPA and HEI staff agree that the following restatements accurately describe each group's position and that they are essentially compatible with each other and with all prior correspondence including the Maxwell letters of March 24 and April 2.

EPA

1. EPA will continue to accept manufacturer statements during Certification regarding the absence of unreasonable risk, for "current" technologies with a history of characterization.

2. EPA expects manufacturers to continue to report annually on their developing technologies and the emissions characteristics thereof. Manufacturers are also expected to request from HEI assessment of the current state of knowledge with respect to a particular pollutant, or new testing of the health effects of the pollutant, for pollutants which may be newly emitted or emitted in larger amounts from a technology with commercial potential. By doing so, they will increase the information available at the time they might seek certification of the technology, and thereby decrease the likelihood that EPA will be unable to decide in favor of certification due to lack of sufficient information.

3. Manufacturer fulfillment of these two expectations does not by itself guarantee that EPA will grant a certificate for a new technology when one is requested. EPA must be able to make a finding or conclusion that there will be no unreasonable risk to public health from the technology. If, despite the manufacturer's annual reports to EPA and requests to HEI, EPA is lacking information to make a finding or conclusion without being arbitrary or capricious, a certificate will not be granted. In the sense of permitting EPA to reach a non-arbitrary/capricious conclusion, the evidence on health effects must be "conclusive".

4. As in the case of Volkswagen's request, EPA may agree to grant a certificate for a small number of model years if the cummulative production will be so small that a finding of no unreasonable risk is possible, to allow for more information to be provided. Manufacturers should not rely upon this possibility, however.

5. In the case of manganese emissions from trap-equipped light-duty vehicles, the October 7, 1985 HEI response to Volkswagen was inadequate for EPA to reach a long-term decision in favor of certification. As noted by HEI, VW had not performed characterization testing to rule out the possibility that the manganese is emitted in an unusual form, i.e., other than as an oxide or elementally. Also, although HEI concluded that there was an absence of studies showing a health effect at expected levels, it provided no affirmative evidence or reasoning as to why an effect was unlikely nor even any clearly stated conclusion or scientific opinion that effects were unlikely. When clear health effects have been demonstrated at higher levels and been accepted by the scientific community, EPA believes that the mere existence of a sizeable difference in concentrations is not enough. Credible inference regarding the lower levels must be based on some additional evidence, such as:

   - a scientifically valid and relevant intermediate-level study with no effect
   - comparison to dietary intake, or to current inhalation exposures from other sources
   - studies on similar compounds
   - knowledge of metabolic pathway or clearance mechanisms.

6. Expert opinion provided through the HEI Committee structure in the absence of definitive data will be highly respected by EPA. EPA expects that such opinions will be clearly stated, with a clear explanation of any computations, assumptions, or judgments used to evaluate the substance in question. Also, the degree of uncertainty should be described, as well as the research program which would better resolve any uncertainty. Of course, EPA and not HEI must make the findings required by the statute.

7. The degree of uncertainty which can be tolerated in making a finding regarding the presence or absence of unreasonable risk depends in part on the cost and time required to remove that uncertainty through additional research.

HEI

1. Inference is often a vital part of the evaluation of the health effects of a substance at a given exposure level. The term "conclusive evidence" is therefore a misnomer.

2. Science cannot provide "conclusive" proof for an absence of health effects. Reliable data on relevant compounds, levels, exposure routes, exposure times, and species accompanied by credible expert inference as to the presence or absence of human health effects under expected exposure conditions can be provided. HEI sees this as part of its role under Section 202(a)(4), since HEI must necessarily consider the available data and form these same inferences when deciding whether and what type of new testing to perform.

3. In addition to being unable to provide "conclusive" proof, science generally does not even yield "conclusive" data. The observations that count as support are themselves dependent on theoretical structures that are subject to change. Furthermore, the sciences that search for adverse health effects (e.g., toxicology and epidemiology) do not yield "conclusive" data that will with total certainty predict that an effect will not occur. With respect to any experiment or study, the risk of a false negative or a false positive is never zero. Nor are there sufficient resources to test for every theoretical possible toxic effect at every possible exposure level under all conceivable sets of experimental conditions. Even if it were possible to achieve all this in animals, extrapolation to humans would still be frought with some uncertainty.

4. HEI has the responsibility, in evaluating evidence and in deciding whether to undertake research, to provide a clear explanation of any computations, assumptions or judgments used to evaluate the particular substance or technology in question, under the intended conditions of use. HEI will clearly distinguish in any analysis between those research recommendations which could refine specific uncertainties about human risk, and those which are important to pursue in order to reach a scientifically defensible judgment about the fundamental nature and extent of human risk.

Table 4

Concentrations of Manganese in Tissues of Man and Animals

Tissue	Manganese Concentration, ppm (fresh-tissue basis)		
	Men	Rabbits	Average for Several Species
Adrenal	0.20	0.67	0.40
Aorta	0.19	–	–
Bones (long)	–	–	3.30
Brain	0.34	0.36	0.40
Heart	0.23	0.28	0.34
Kidney	0.93	1.20	1.20
Liver	1.68	2.10	2.50
Lung	0.34	–	–
Muscle	0.09	0.13	0.18
Ovary	0.19	0.60	0.55
Pancreas	1.21	1.60	1.90
Pituitary	–	2.40	2.50
Prostate	0.24	–	–
Spleen	0.22	0.22	0.40
Testis	0.19	0.36	0.50
Hair	–	0.99	0.80

Source: NRC, 1973

Table 5: Manganese in Foods

Food	Manganese (wet weight, µg/g)	Food	Manganese (wet weight, µg/g)
Whole wheat, seed	11.32	Raisins, package	4.68
Bread, white	1.78	Apple	0.31
Bread, whole wheat	1.43	Orange	0.35
Oatmeal	2.72	Peach	1.02
Corn meal	2.05		
Macaroni, dry	10.56	Pecans	35.09
Grapenuts	30.76	Peanuts, salted	6.91
Milk, whole	0.19	Spinach, fresh	7.77
Milk, dry skimmed	0.00	Beets, fresh	0.41
Butter	0.96	Beans, canned	0.24
Eggs, whole	0.53	Peas, fresh	0.64
		Tomatoes, canned	0.30
Beef, roasting	0.05		
Lamb chops, lean	0.34	Black pepper	47.48
Chicken breast	0.21	Cloves	262.86
		Garlic powder	0.45
Halibut steak	0.12	Coffee, ground	20.65
Scalloos, fresh	0.11	Coffee, infusion	0.85
Clams, fresh frozen	0.00	Tea, leaves	275.58
		Tea, infusion	6.9
Cod liver oil	4.95		
Corn oil	1.00		
Safflower oil	0.00		

from: Cooper, 1984

From: U.S. EPA 1984

TABLE 6

Respiratory Effects with Manganese Exposure: Inhalation Exposures at Low Doses

Species	Compound	Concentration (particle size)	Exposure	Effects: Mn Only	Effects: Mn + Bacteria	Effects: Bacteria Only	Comments	Reference
Mice, Charles River, CD-1 (20-195/group)	Mn_3O_4 aerosol	897 µg/m³ (1-3 µm)	2 hours	-	NS	NS	Normal cell concentration (macrophages, PMNs, lymphocytes). No increase in extracellular protein (no edema). No effect on phagocytic capability.	Adkins et al., 1980b
Mice, Charles River, CD-1 (20-41/group)	Mn_3O_4 aerosol	220-2650 µg/m³ (1-3 µm)	2 hours	NS	++	+	(Bacteria only = control) Mean mortality rate increases over controls as Mn concentration increases. Enhanced growth of streptococci over controls.	Adkins et al., 1980c
Rats, Sprague-Dawley (30/group) Monkeys, squirrel (8/group)	Mn_3O_4 particulate	Control 11.6 µg 112.5 µg 1152 µg (<2 µm)	24 hours/day, 9 months	-	NS	NS	No exposure related gross or microscopic alterations or effects on mechanical or ventilatory properties of the lung. (No exposure related effect on EMG or limb tremor.	Ulrich et al., 1979a,b,c
Monkeys, Rhesus (7 exposed, 5 controls)	Mn_3O_4 particulate	100 µg/m³	24 hours/day to 66 weeks	-	NS	NS	No abnormal changes seen on gross or microscopic examinations. Increase of Mn in lung. 8/12 had acariasis.	Coulston and Griffin, 1977
Monkey, Rhesus A) 3 exposed B) 2 exposed	MnO_2 dust	A) 3000 µg/m³ B) 700 µg/m³	22 hours/day, 10 months	+	NS	NS	Inflammatory changes earlier in A than B; granular rather than infiltrative shadows. After 10 months hyperplasia of lymphoid tissue, pulmonary emphysema. Deposits of dust in macrophages.	Suzuki et al., 1978
Rats (74/group) Hamsters, golden (60/group)	Automotive emissions containing Mn	117-131 µg/m³ (0.3 µm) plus other particulate and gases	8 hours/day, 56 days	-	NS	NS	No gross or microscopic changes in the lung.	Moore et al., 1975

NS = Not studied

Table 7*

RESULTS OF VOLKSWAGEN MODELING

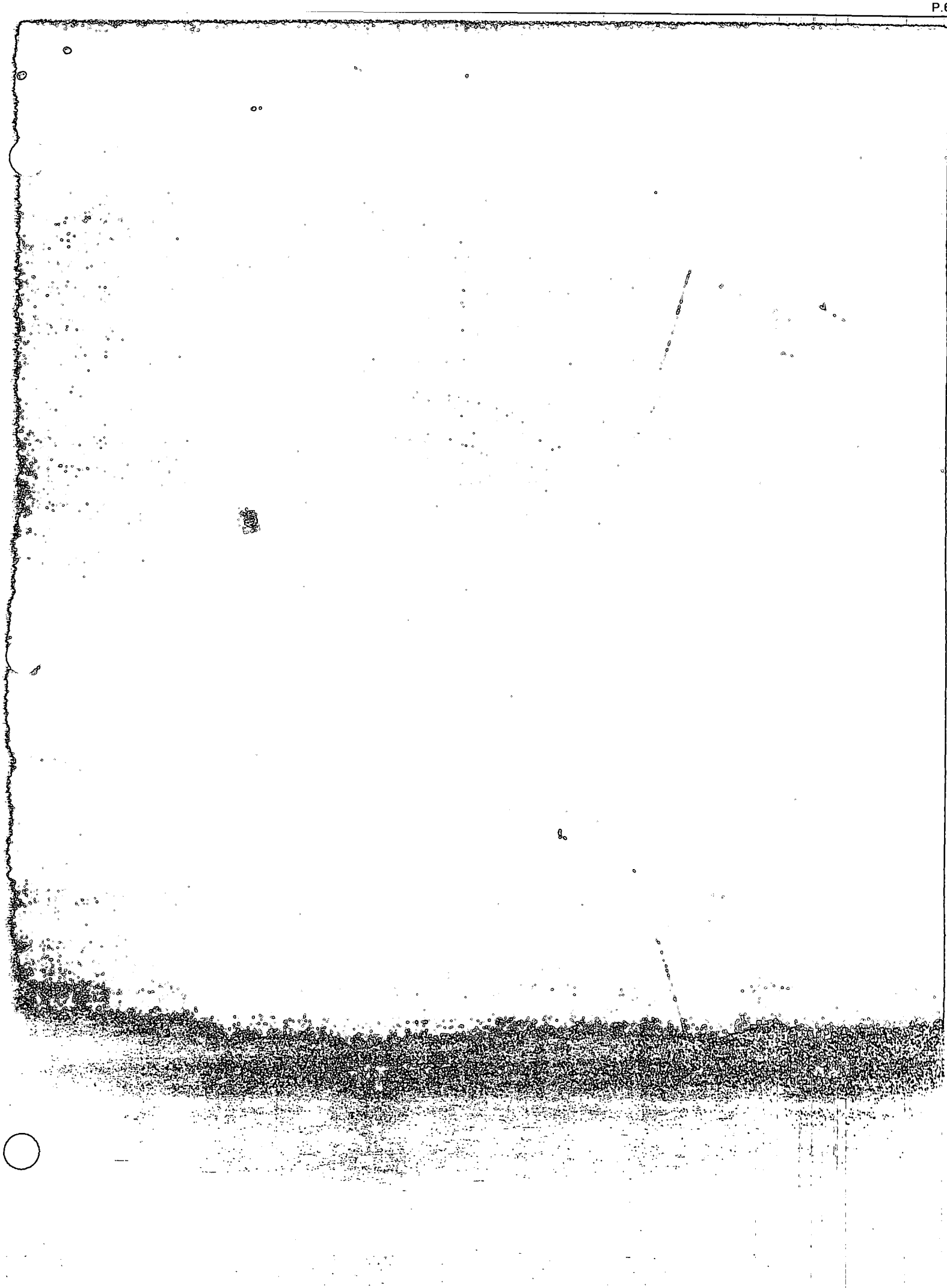
Roadway	Emission rates (mg Mn/mi)	Roadside concentration (ug Mn/m^3)
Highway	4.00	1.98
	1.38	0.64
Street Canyon	10.00	7.60
	3.13	2.20

* From Volkswagen (1984).

Table 8

ESTIMATED AMBIENT Mn CONCENTRATIONS DOWNWIND OF A HIGHWAY
(100% penetration)

Wind Direction to Roadway	Emission Rates (mg Mn/mile)	Estimated Concentrations 4m Dnwnd (ug Mn/m^3)	100m Dnwnd (ug Mn/m^3)
Volkswagen Analysis			
90°	4.00	1.98	0.84
90°	1.38	0.64	0.22
HEI Analysis			
90°	4.00	2.00	0.80
90°	1.38	0.68	0.29
45°	4.00	2.50	1.20
45°	1.38	0.87	0.39
5°	4.00	3.60	2.50
5°	1.38	1.14	0.87



ATTACHMENT A

VOLKSWAGEN OF AMERICA, INC.

888 W. Big Beaver
P.O. Box 3951
Troy, Michigan 48007-3951
Tel. 313/362-6000
Western Union Telex 230 628

June 29, 1984

Charles W. Powers
Health Effects Institute
215 First Street
Cambridge, Massachusetts 02142

Dear Mr. Powers:

As you are well aware, the U.S. Environmental Protection Agency (EPA) and California Air Resources Board will require manufacturers to meet reduced diesel particulate emission standards in future model years. The imposition of these low emission standards will require the installation of new, sophisticated emission control hardware capable of reducing engine-out diesel particulate levels. The favored approach for control of the engine-out emissions is the use of a diesel particulate trap and a system to regenerate the trap after it has become filled with particulate matter. A variety of regeneration systems are under consideration. Their function is to burn the particulate matter that has been deposited on the trap. This may be accomplished using a number of methods including external burners, catalytically coated traps, and fuel additives. Volkswagen's most promising system uses the fuel additive method. A fuel additive injected into the fuel system has the effect of lowering the ignition temperature of the diesel particulate matter collected on the trap and aids in the burning process. Volkswagen has found that for our systems, manganese compounds (manganese-containing fuel additives) provide a suitable means for regeneration.

As an unregulated substance, it is necessary, according to the Clean Air Act, to make an assessment of whether manganese emissions pose a risk to public health. Volkswagen, therefore, has compiled an analysis of the manganese concentrations in ambient air which may be expected with the introduction of manganese-containing additives for diesel fuel. The estimated concentrations are compared to the threshold values for possible health effects. Further, under contract with Volkswagenwerk AG, the Fraunhofer Institute conducted a literature search to evaluate the health effects associated with the use of a manganese additive for diesel particulate trap regeneration. Both the ambient air analysis and health effects literature search are contained in the enclosed research report.

A review of the report reveals a comprehensive determination of estimated ambient levels of manganese and that available health effects data has been summarized. There is some concern however, that there is a paucity of inhalation health data of manganese at the lower levels (e.g., 0.01 mg/m^3). In view of this lack of information, Volkswagen is requesting the assistance of the Health Effects Institute (HEI).

More specifically, we request that the HEI address our concerns by determining whether the assessment of health data at low levels of manganese is warranted. The research report enclosed provides a summary of the data available thus far and therefore indicates the point above which the health effects are known. These implied limits may be useful in the assessment. It should be noted that the more stringent diesel particulate standards, those which make the control systems in question necessary, are applicable beginning with the 1985 model year in California and 1987 model year Federally. The urgent need for an assessment is therefore obvious.

Volkswagen would greatly appreciate your presentation of our request to the Health Research Committee. The emission control system and particularly the use of fuel additives described above certainly represents new developments in automotive technology. As such, a change in the unregulated substances emitted may be expected, albeit at low levels. HEI has stated in the past, and most recently at the last HEI sponsors meeting in Ann Arbor that new development in technology and the resultant change in substances emitted is justification for future HEI consideration. Based on that premise, Volkswagen believes that an assessment, by HEI, of the need for health data associated with lower level concentrations of manganese used as a diesel fuel additive is both necessary and warranted.

Your assistance in this matter is greatly appreciated.

Best regards,

W. Groth

Wolfgang Groth
Manager
Emissions & Fuel Economy
LWK/cs

Enclosure

ATTACHMENT B

HEALTH EFFECTS INSTITUTE

215 First Street
Cambridge, Massachusetts 02142
(617) 491-2926

October 7, 1985

Mr. Wolfgang Groth
Manager, Emissions and Fuel Economy
Volkswagen of America, Inc.
888 W. Big Beaver
P.O. Box 3951
Troy, Michigan 48007-3951

Dear Mr. Groth:

In a letter to the Health Effects Institute (HEI) dated June 29, 1984, Volkswagen Of America, Inc. requested that the HEI Health Research Committee undertake an evaluation of potential health issues related to emissions from diesel automobiles using manganese(Mn)-containing fuel additives for particle trap regeneration. As indicated in our initial response of July 23, 1984, your request was brought to the Research Committee at its next meeting, which occurred in September 1984. Since then, significant work has been underway.

This letter summarizes the HEI's response to Volkswagen and includes a discussion of the known health effects of manganese in the context of increased ambient levels of Mn expected with implementation of the trap technology. Prior to the technical summary, we briefly discuss the statutory and institutional frameworks for our response and the process leading to this evaluation.

Framework and Process

The Volkswagen (VW) request is relevant to both compliance of automobile manufacturers with the Clean Air Act (CAA) and to the chartered role of the Health Effects Institute. Section 202(a)(4) of the Act states that "no emission control device, system or element of design shall be used in a new motor vehicle or new motor vehicle engine for purposes of complying with standards prescribed under this subsection if such device, system, or element of design will cause or contribute to an unreasonable risk to public health, welfare, or safety in its operation or function."

The manganese additive in question is a key ingredient in a new technology designed to lower diesel particulate emissions in

compliance with Federal and California State law. As such, this technology is covered by Section 202(a)(4) of the Clean Air Act. Volkswagen's concern to remain in compliance and its request to the HEI is appropriate.

The Health Effects Institute operates under the joint sponsorship of the Environmental Protection Agency (EPA) and the motor vehicle industry to support health research on automotive emissions. The HEI undertakes research and evaluations in an attempt to develop an objective and commonly accepted database. In a letter dated March 20, 1984 to all motor vehicle and engine manufacturers, Joseph Cannon, the EPA Assistant Administrator for Air and Radiation, and Bernard Goldstein, the EPA Assistant Administrator for Research and Development, jointly reaffirmed the Health Effects Institute as "the primary mechanism through which participating motor vehicle manufacturers discharge their health testing responsibilities under Section 202(a)(4) of the Clean Air Act." They further urged "that unregulated emissions of potential importance be brought to the Health Effects Institute's attention in a timely manner."

In order to meet its obligation to its sponsors, and fulfill its role in helping to implement Section 202(a)(4) of the Clean Air Act, the HEI conducted an evaluation of manganese under the supervision of the Health Research Committee. In its September 1984 meeting, the Committee discussed the VW request and received a preliminary briefing on the toxicology of manganese from Dr. Carl Shulz (COSAR, Inc.). The Committee accepted the VW request and decided that further analyses were necessary to determine if the tailpipe emissions of Mn were of public health concern and whether the HEI should sponsor research in this area. Following this meeting, the HEI commissioned Roth Associates (Dr. Neil Roth, PI) to conduct an in-depth review of the relevant literature on manganese. This review included actual replication of Volkswagen's modeling predictions on potential Mn-exposure levels from the regenerator, additional modeling of other emission scenarios not analyzed by VW, plus analyses of the health effects literature. The Committee evaluated all of this information at its June 1985 meeting. A final review of the information in this letter was conducted at the Committee's meeting on September 26, 1985.

Summary of Evaluation

The evaluation first places projected Mn emissions in the context of ambient Mn levels across the United States, and then examines the health literature on Mn to establish whether the expected incremental levels of airborne Mn from regenerator-equipped automobiles are of health-related concern. Finally, we identify a number of areas in which our knowledge concerning exposure and potential effects can be improved.

To summarize our findings, increased air concentrations of Mn resulting from the use of VW's particle trap will not, under

any realistic scenario, reach the lowest concentrations that have been reported in the literature to be associated with adverse chronic health effects. Despite this conclusion, certain gaps remain in our knowledge of Mn emissions and effects. These gaps primarily involve the particle size distribution and chemical species (e.g., MnO_2, Mn_3O_4) in which Mn is emitted and how they might affect toxicity. The gaps in emissions characterization are best dealt with by the manufacturers directly as more experience is obtained.

Manganese: Ambient Levels and Automobile Emissions

Manganese is the twelfth most abundant element on earth, and is found mainly in oxide or carbonate form as a natural constituent of soil and water. As such, Mn is a component of background aerosol that winds, waves, and other natural processes generate. Manganese is also found in a wide variety of foods (Table 1), and is considered essential for normal health. Food accounts for at least 98% of an adult person's intake of manganese (2-9 mg Mn/day) with practically all the remainder in drinking products; inhalation, in all but the most polluted occupational settings, contributes negligibly to the body burden of Mn.

Monitoring of ambient manganese in the United States started in 1953. As a general trend, Mn levels have decreased since that time and have remained relatively stable since 1972. Improved industrial control processes are believed to account for much of the decrease. Quarterly data collected by the National Air Surveillance Network (NASN) show that between 1972 and 1982 in urban sites, the highest median level of Mn for any year was 0.034 ug Mn/m^3 (1978), and the highest 95^{th} percentile level was 0.12 ug Mn/m^3 (1972); corresponding values for nonurban NASN sites are a median of 0.009ug Mn/m^3 (1977) and 95^{th} percentile of 0.030 ug Mn/m^3 (1976,1977).[10] These data, though valuable, are regional and tend to obscure the higher local Mn levels that may result, for example, from industrial activity, quarrying processes, or farming. For example, near foundries, Mn levels can typically reach 0.3 ug/m^3, and near ferromanganese plants, they can exceed 1 ug/m^3. EPA Storage and Retrieval of Aerometric Data (SAROAD) collected from 1980 to 1982 (Table 2) show that many areas experience peak 24-hour Mn levels in excess of 0.1 ug/m^3, and that locations in three states (Indiana, Maryland, and Pennsylvania) registered mean 24-hour averages greater than 0.1 ug Mn/m^3.

The highest exposures to airborne manganese occur occupationally in mining operations, ore processing plants, and ferromanganese plants (Table 3). The levels in these settings may be a thousand times or more greater than the higher ambient urban levels discussed earlier. In recognition of the potential toxicity of manganese at these extreme occupational levels, workplace standards have been set (Table 4). The World Health Organization's is the most conservative at 300 ug Mn/m^3 time-

weighted average. In interpreting the meaning of this level, it is important to bear in mind that a workplace standard applies to a workforce that is presumed healthy and more resilient to environmental insult than the population at large. Workplace standards are not applicable to the general public, and should not be construed as protective of the public's health.

Without the use of manganese fuel additives, the contribution of motor vehicle emissions to ambient manganese levels is probably very small. In the 1970's, MMT, a Mn-containing additive was included in some unleaded gasolines to improve octane ratings. Consequently, some efforts were taken to estimate and measure the increased Mn concentrations in air associated with the additive's use. Ter Haar et al (1975) estimated that the mean urban increment would be 0.05 ug Mn/m^3 with a peak of 0.25 ug Mn/m^3 if MMT was in all vehicles and fuel concentrations of Mn were 0.125 g/gal.[9] Pierson et al (1978) with the use of aerosol sampling, determined Mn levels in the Allegheny and Tuscarora Tunnels of the Pennsylvania Turnpike for several one-week intervals between 1975 and 1977.[7] (In this period, the use of MMT was at its peak; however, in 1978, the use of MMT as an additive to unleaded gasoline was terminated.) The highest average weekly level inside the tunnels was 0.13 ug Mn/m^3, and the average for the measurement periods was 0.11 ug Mn/m^3. The peak use of MMT during the study (1977) resulted in an average value of 16 mg Mn per gallon of gasoline in vehicles coursing through the tunnels; corresponding Mn-emission rates were 0.13 mg Mn/mile. These data suggest that in locations with a heavy flow of traffic emitting MMT-derived manganese into a confined space, increased manganese levels at roadside may be discriminated from background levels. One of the important unknowns, and a possible confounding factor in roadside measurements, is the extent to which traffic resuspends road dusts that contribute to the manganese content of the roadside aerosol.

Volkswagen has proposed to equip its diesel automobiles with a particle regenerator system that uses Lubrizol 8220, a manganese-containing additive. The system is designed to help model 1986 and future automobiles comply with U.S. and California regulations for particulate emissions. The emission rates of manganese from vehicles so equipped are expected to be considerably higher than those associated with MMT use. For highway driving, VW estimates that emission rates will range from an expected value of 1.38 mg Mn/mile to a worst-case value of 4 mg Mn/mile; For street driving, expected emissions will be 3.13 mg Mn/mile with a worst-case value of 10 mg Mn/mile.[17,18] (VW had previously estimated that conservatively, Mn emissions from MMT could be 0.58 mg Mn/mile.[5]) The worst-case numbers are based on the assumption that all of the manganese metered into the fuel stream is emitted while the expected values reflect realistic Mn retention in the engine and particle filter.

Volkswagen has used modeling techniques to project these emission rates into manganese concentrations at the side of freeways and within street canyons. Assuming 100% penetration of the regenerator into the automobile fleet, worst-case traffic conditions, and a crossroad wind, VW calculated,using the EPA HIWAY-2 model, the Mn concentrations indicated in Table 5.

The data obtained from such modeling calculations are necessary and important for placing the health questions in the perspective of expected human exposure. The necessity derives from the fact that direct measurements of manganese are not now possible since the technology is not yet implemented in the active fleet. The modeling results are important because they help anticipate whether situations may arise in which manganese concentrations achieve levels that are associated with known health effects. Given these considerations, the HEI felt it appropriate to independently verify the results from the HIWAY-2 model. The HEI analyses basically agree with VW's results except that, for highways,the most conservative values occur with the wind parallel to the roadway (Table 6). With a parallel wind (5 degrees to the roadway) VW's worst-case highway Mn level would be 3.60 ug Mn/m^3 instead of 2.00 ug Mn/m^3.

These modeling exercises produce ceiling estimates based on hypothetical situations. These estimates serve a valuable purpose in that, once accepted, they provide a reference for applying correction factors. Perhaps the most important correction factor involves fleet penetration of the manganese technology. The California Air Resources Board (CARB) estimates that by 1990, between 2.6% and 6.6% of the vehicle fleet will have particle traps (values derived from reference #1, Table 1). Thus, for 1990, one may adjust the worst-case street canyon value of 7.6 ug Mn/m^3 to between 0.2 and 0.5 ug Mn/m^3 for upper-bound emission rates of 10 mg Mn/mile, and to between 0.06 and 0.16 ug Mn/m^3 for expected emission rates of 3.13 mg Mn/mile. Likewise, for highways with parallel winds, Mn values at roadside will be between 0.09 and 0.24 ug Mn/m^3 for upper-bound emission rates of 4 mg Mn/mile, and between 0.03 and 0.08 ug Mn/m^3 for expected emission rates of 1.38 mg Mn/mile.

It seems highly unlikely, therefore, that, under the conditions described, automobiles equipped with the proposed particle regenerator system will contribute more than 1 ug Mn/m^3 to ambient air. A number of factors, however, still require attention to provide a more complete picture of manganese emissions from these automobiles. At present there is no information on the size distribution of Mn-containing particles in the exhaust or the species of manganese compounds that are emitted. Also, the modeling performed to date does not consider the mode of vehicle operation such as acceleration and steady state driving.— If the properties of Mn emissions are similar to those of lead, then the percentage of Mn exhaust may vary with the vehicle operating condition and will increase when vehicles accelerate from a stop or a low cruise (20 mph) to a much higher

speed (60 mph). This occurs because particles can build up in the exhaust system during steady state driving and are released during high load accelerations. If this is the case, then the roadside levels of Mn at a section of road where vehicles accelerate will be higher than the above calculations indicate.

Health Effects of Manganese

At present, there is no indication that health effects are associated with chronic exposures of less than 2 ug Mn/m^3, a value we believe exceeds the highest ambient levels expected with use of the regenerator. The effects of greatest concern are neurotoxic and respiratory and these have been reported over the past several decades in studies of occupational exposure to manganese. There are no studies which have investigated whether inhaled manganese is carcinogenic in laboratory animals or human beings. Manganese administered by subcutaneous, intraperitoneal, or intramuscular routes has induced tumors in some studies but not in others (reviewed in reference #12). Inhalation studies have concentrated primarily on neurotoxic and respiratory effects.

Neurotoxicity: The neurotoxic effects in humans require at least several months of exposure and progress from an early reversible stage characterized by psychological disturbances to a more advanced and irreversible stage marked by a neuropathy that has been labeled manganism. This condition resembles Parkinsonism in its overt manifestations of a motor disorder, and like Parkinson's disease, does involve neural pathways in the brain that utilize the neurochemical transmitter, dopamine. However, the specific regions of the brain relevant to each of the two diseases are different.

The human clinical and epidemiologic literature suggests that neurotoxicity is not strongly indicated until exposure exceeds 5 mg Mn/m^3 (or 5,000 ug Mn/m^3), but that neurological symptoms may occur at levels as low as 0.3 mg Mn/m^3 (300 ug Mn/m^3). A possible exception is a study in which Saric et al (1977) compared neurologic symptoms among workers in a ferroalloy plant (0.3-20.4 mg Mn/m^3), an electrode plant (2-30 ug Mn/m^3) and an aluminum rolling mill (0.05-0.07 ug Mn/m^3), the last to serve as a control.[8] Their findings show an excess of symptoms in the ferroalloy plant and a smaller excess in the electrode plant, suggesting an effect between 2 and 30 ug/m^3. This study, however, suffers from serious inadequacies. The symptom of major importance in the electrode plant, tremor at rest, is not attributable solely to manganese and possible confounding factors were not studied. Secondly, a number of subjective symptoms did not follow a dose-response relation across the three plants, and also failed to do so when the ferroalloy cohort was sub-divided into three exposure groups. Finally, statistical analyses of the published data were conducted for the HEI (Roth Assoc.) and show that smoking alone may explain the differences in symptoms between plants.

Animal studies shed little additional light on the subject. Only two studies have attempted to study neurological or behavioral effects following inhalation of manganese aerosol. In neither case were effects reported in monkeys at concentrations of Mn_3O_4 ranging over $1mg/m^3$.[3,14-16]

Respiratory Toxicity: The respiratory effects of manganese involve an inflammatory effect or pneumonitis, which may lead to diminished pulmonary function, bronchitis, or altered susceptibility to infection. The animal research literature suggests that chronic pulmonary effects may occur between 100 and 700 ug/m^3. As with the research on neurotoxicity, the literature is limited and difficult to extrapolate to manganese emissions from automobiles.

The U.S. EPA, in its Health Assessment Document for Manganese, considers respiratory symptoms to be the "critical effect" for manganese because respiratory effects are reported at levels lower than those reported for neurotoxicity. Based on studies in rats and monkeys, the EPA calculated Human Equivalent Exposure Levels (HEEL) for studies indicating No Observed Effect Levels (NOEL) and the Lowest Observed Adverse Effect Level (LOAEL). After applying a correction factor of 10 to account for potentially sensitive individuals, the EPA derived a human equivalent NOEL of 5 ug Mn/m^3 based on rats and 8.7 ug Mn/m^3 based on monkeys; the LOAEL, based on monkeys is 36.5 ug Mn/m^3.[13]

These levels are much lower than those associated with respiratory effects in occupational settings. The studies of workers exposed to manganese generally show that respiratory effects follow exposures in excess of 5 mg Mn/m^3. There are data, however, from a Japanese study (Nogawa et al, 1973) of junior high school students that apparently associate increased respiratory symptoms and diminished pulmonary function with manganese levels in the NOEL-LOAEL range that EPA calculated.[6] The major variable in the study was proximity of the student's school to a source of ambient manganese. The source was a ferromanganese plant and the students classified as "exposed" attended a school 100 meters from the plant. Students in a school 7 km from the plant served as controls. Relative exposure of the two groups to manganese was primarily determined by the amount of manganese in the dustfall at the two locations. The investigators estimate that exposure near the plant was 20 or more times higher near the plant than at the control site. Air samples that were taken 100 m from the plant indicated airborne manganese concentrations of 4 ug Mn/m^3. EPA estimated, on the basis of analyses of dustfalls near a ferromanganese plant in the Kanawha Valley in West Virginia, that the dustfall in the Nogawa study may translate to between 3 and 11 ug Mn/m^3.[11]

Although participation of the student bodies in the survey was nearly complete, several problems remain which prevent this study from being conclusive. First, dustfall was used by the investigators as the principal index of exposure rather than

direct air sampling. It is thus difficult to ascertain the amount of dust that, when suspended, contained respirable manganese. The quality of exposure information, therefore, is less than desirable. Also, the authors failed to adjust for potential socio-economic factors. Frequently, poorer populations with inferior health and medical care are located in more heavily polluted areas. Associated environmental conditions may include increased crowding at home and increased exposure to indoor pollutants, particularly, cigarette smoke. Such factors may bias resulting health data and produce inappropriate conclusions. Furthermore, pulmonary function was not tested in a blind fashion, nor did the investigators appear to have a full appreciation of the difficulty in administering pulmonary function tests to school children. In addition, there are problems with the study's medical questionnaire, an adaptation of the British Medical Research Council's Questionnaire (1966 version). It primarily probed for subjective responses, an approach that is difficult to control even in studies of adults.

Thus, despite the relevance of the exposure levels in this study to worst-case manganese levels expected from automobile emissions, we believe the data are subject to question. Nonetheless, the study stands as the only one on record that addresses potential chronic effects of low levels of manganese in a potentially sensitive segment of the non-occupationally exposed population. The criticism given above suggest that the study suffers from methodologic deficiencies, but they do not invalidate the reported results. The ambient concentrations of manganese apparently associated with respiratory effects in this study are, according to estimates and limited measurements, 3 to 4 times higher than the the maximum concentrations expected from diesel automobiles under realistic scenarios. However, there are no epidemiologic data from the general population that have examined for respiratory effects at lower levels.

Conclusion

The available data do not indicate that currently anticipated levels of manganese emissions from diesel automobiles using Lubrizol 8220 are associated with increased public health risks. It appears unlikely that implementation of the regenerator, as currently proposed by Volkswagen, will result in an increase of more than 1 ug Mn/m^3 in ambient air; airborne manganese concentrations from other sources rarely exceed 0.1 ug Mn/m^3. Inhaled manganese is capable of producing health effects, specifically neurotoxic and respiratory, but none of these have been demonstrated at the maximum ambient levels expected with implementation of the trap technology into the light duty fleet. Despite an apparent margin of safety between maximally expected manganese concentrations and the lowest levels at which effects may occur, additional information is necessary to reinforce a conclusion that no health effects are expected.

We presently lack data on the size distribution of particles emitted from the tailpipe and the amount and species of manganese they contain. According to VW analyses, the manganese is likely to be in oxide form (e.g., MnO_2, Mn_3O_4), but measured values of species-specific manganese levels in diesel exhaust are not yet available. These data are important because particle size distribution helps predict the extent and region of pulmonary particulate deposition, and a description of the chemical form of emitted manganese is important in case its toxic effects are a function of its valence state. The Health Research Committee believes that Volkswagen must continue its efforts to characterize tailpipe emissions over a range of engine operating modes, and to communicate the data to all interested parties.

As discussed in this letter, the data base on the health effects of manganese is not as complete as one would prefer. Because manganese is essential for normal health, it is reasonable to expect that there are threshold levels below which health effects are not expected. The range of that threshold and how it may vary for different subpopulations are not currently known with any accuracy. With the exception of the study by Nogawa et al, the available evidence does not implicate manganese in adverse effects until it achieves levels between 100 and 1000 micrograms per cubic meter; using CARB estimates for fleet penetration of the trap technology, ambient levels of Mn will remain below 1 ug Mn/m^3. As mentioned, the Nogawa study cannot be overlooked despite its methodological problems, and perhaps a reanalysis of the study design and raw data would clarify its results.

The EPA issued a decision on August 13, 1985 not to regulate manganese as a hazardous air pollutant under Section 112 of the Clean Air Act.[4] However, the Agency also intends to continue to monitor research activities, "and will reinstitute assessment if warranted by the results of that research." The Health Effects Institute endorses such flexibility and stands ready to reevaluate this issue as new relevant scientific and engineering data emerge or the use of the manganese technology expands beyond currently anticipated levels.

Please feel free to contact the HEI if you have further questions concerning the issues in this letter or any new concerns that may arise. We thank you for your interest.

Sincerely,

Thomas P. Grumbly
Executive Director

cc: HEI Health Research Committee
Mr. Stanley Blacker

REFERENCES

1. California Air Resources Board, Memorandum-"Modeling Analysis of Potential Impacts of Manganese as a Diesel Fuel Additive", Sacramento, CA, September 20, 1984.

2. Cooper, W.C. 1984. The health implications of increased manganese in the environment resulting from the combustion of fuel additives: A review of the literature. J. Toxicol. Environ. Health 14:23-46.

3. Coulston, F., and Griffin, T. 1976. Inhalation toxicology of airborne particulate manganese in rhesus monkeys. Institute of Comparative and Human Toxicology, International Center of Environmental Safety, Albany Medical College, Holloman Air Force Base, New Mexico. EPA Contract No. 68-02-0710. (Also EPA-600/1-77-026, May 1977.)

4. Environmental Protetion Agency. Decision Not to Regulate Manganese Concentrations as Hazardous Air Pollutant Under Section 112 of Air Act. Federal Register 50: 32627-32628, August 13, 1985.

5. Fraunhofer-Institut fur Toxikologie und Aerosolforschung Institutsteil, Hannover/Munster. Evaluation of Health Effects Associated with the Diesel Trap Oxidizer Regeneration, A Literature Search. Under contract with Volkswagenwerk AG. February 1984. p.13.

6. Nogawa, K., Kobayashi, E., Sakamoto, M., Fukushima, N., Ishizaki, A., Makino, N., Kagamimori, S., Hiramaru, Y., Kawano, S., Kato, T., Kanekawa, KJ., Shozo. 1973. Studies of the effects on the respiratory organs of air pollution consisting of dusts composed mainly of manganese. (First Report) Effects on the respiratory organs of junior high school students. Nippon Koshu Eisei Zasshi (Jap. J. Public Health) 20:315-325.

7. Pierson, W.R., McKee, D.E., Brachaczek, W.W., and Butler, J.W. 1978. Methylcyclopentadienyl manganese tricarbonyl: Effect on manganese emissions from vehicles on the road. J. Air Pollut. Control Assoc. 28:692-693.

8. Saric, M., Markicevic, A., and Hrustic, O. 1977. Occupational exposure to manganese. Br. J. Ind. Med. 34: 114-118.

9. Ter Haar, G.L., Griffing, M.E., Brandt, M., Oberding, D.G., and Kapron, M. 1975. Methylcyclopentadienyl manganese tricarbonyl as an antiknock: Composition and fate of manganese exhaust products. J. Air Pollut. Control Assoc. 25:858-860.

10. United States Environmental Protection Agency, Environmental Criteria and Assessment Office. Health Assessment Document for Manganese. Final Report. EPA-600l8-83-013F. August 1984. pp. 3-67 to 3-68.

11. Ibid p. 6-52.

12. Ibid pp. 7-1 to 7-11.

13. Ibid pp. A-1 to A-5.

14. Ulrich, C.E., Rinehart, W., and Busey, W. 1979. Evaluation of the cronic inhalation toxicity of a manganese oxide aerosol. I. Introduction, experimental design and aerosol generation methods. Am. Ind. Hyg. Assoc. J. 40:238-244.

15. Ulrich, C.E., Rinehart, W., Busey, W., and Dorato, M.A. 1979. Evaluation of the cronic inhalation toxicity of a manganese oxide aerosol. II. Clinical observations, hematology, clincial chemistry and histopathology. Am. Ind. Hyg. Assoc. J. 40:322-329.

16. Ulrich, C.E., Rinehart, W., and Brandt, M. 1979. Evaluation of the cronic inhalation toxicty of a manganese oxide aerosol. III. Pulmonary function, electromyograms, limb tremor, and tissue manganese data. Am. Ind. Hyg. Assoc. J. 40:349-353.

17. Volkswagen, Manganese Concentrations in Air Resulting from the Possible Use of Manganese Compounds as a Diesel Fuel Additive and Health Effect Aspects of Manganese, Wolfsburg, West Germany, March 13, 1984.

18. Wiedemann B., and Neumann, K.H. 1985. Vehicular experience with additives for regeneration of ceramic diesel filters, Volkswagenwerk AG, Wolfsburg, West Germany, SAE Technical Paper Series No. 850017, Warrendale, PA.

Table 1

Manganese in Foods[a]

Food	Manganese (wet weight, μg/g)	Food	Manganese (wet weight, μg/g)
Whole wheat, seed	11.32	Raisins, package	4.68
Bread, white	1.78	Apple	0.31
Bread, whole wheat	1.43	Orange	0.35
Oatmeal	2.72	Peach	1.02
Corn meal	2.05		
Macaroni, dry	10.56	Pecans	35.09
Grapenuts	30.76	Peanuts, salted	6.91
Milk, whole	0.19	Spinach, fresh	7.77
Milk, dry skimmed	0.00	Beets, fresh	0.41
Butter	0.96	Beans, canned	0.24
Eggs, whole	0.53	Peas, fresh	0.64
		Tomatoes, canned	0.30
Beef, roasting	0.05		
Lamb chops, lean	0.34	Black pepper	47.48
Chicken breast	0.21	Cloves	262.86
		Garlic powder	0.45
Halibut steak	0.12	Coffee, ground	20.65
Scallops, fresh	0.11	Coffee, infusion	0.85
Clams, fresh frozen	0.00	Tea, leaves	275.58
		Tea, infusion	6.9
Cod liver oil	4.95		
Corn oil	1.00		
Safflower oil	0.00		

[a]Selected from Schroeder et al. (1966), Table 6, pp. 551-552.

from Cooper, 1984

ATTACHMENT B-3

Letter from Herschel E. Griffin, M.D.
and Norton Nelson, Ph.D.
to the Hon. William D. Ruckelshaus

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
THE ADMINISTRATOR

Hon. William D. Ruckelshaus
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Mr. Ruckelshaus:

The Environmental Health Committee of EPA's Science Advisory Board has completed its review of the Health Assessment Document for Manganese, prepared by the Office of Health and Environmental Assessment (OHEA) in EPA's Office of Research and Development [EPA-600/8-83-013; June, 1983; External Review Draft]. The draft document was prepared for Agency-wide use to place health effects associated with this pollutant in perspective. It will serve specifically as a scientific basis for regulatory decisions by the Office of Air and Radiation.

The Committee referred the task of preparing its report to its Metals' Subcommittee. The latter panel met for this purpose on October 23, 1984, and its report is attached to this letter. The Committee fully concurs with the Subcommittee's evaluation.

The Committee agrees with the major conclusions in the draft health assessment document. Specifically, it concurss with the position that manganese is associated with two health effects in humans. These include:

(1) pulmonary symptoms, defined as either an inflammatory response at high manganese exposures or an increased susceptibility to pulmonary diseases with low, chronic manganese exposures.

(2) neurological signs and symptoms characterized by both psychiatric and movement disorders.

The Committee questions the document's conclusion, however, that pulmonary effects occur at lower exposures than do neurologic effects.

In addition, the Committee finds evidence that manganese may be a mammalian mutagen, according to the criteria established by the National Academy of Sciences. Although manganese is an essential trace element, the literature does not indicate whether or not inhaled manganese contributes to nutritional needs.

At the time of its review the Committee suggested that OHEA staff obtain more detailed technical comments from individual members. Following this consultation, the Committee agreed to prepare a formal report of its scientific review of the document. In addition to these consultations, the revisions to which OHEA staff agreed to make on November 10, 1983 include:

(1) to reorganize the review of neurotoxic effects with a more critical viewpoint, and to insure that the document is consistent with the current neuroscience data and literature.

(2) to focus attention on the few studies in which both pulmonary and neurotoxic effects were examined.

(3) to provide diagrams of nervous system structures and processes deemed to be the sites of manganese neurotoxicity.

(4) to define better the biologic nature of the nervous system effects of manganese (so-called manganism), which was treated inconsistently in the text.

(5) to incorporate the information from several papers not referenced in the document, as suggested by the Committee. These papers are described in the enclosed technical comments.

(6) to provide additional information in those tables summarizing health effects. The new information would set out:
(a) the nature of the effect, in brief descriptive terms.
(b) the minimum level of exposure that led to the observation of statistically significant health effects, if effects were observed.
(c) the maximum level of exposure that produced no significant effects, if any levels of exposure did not elict health effects.

Additional technical comments are reported in the attached paper. A separate set of comments from individual Committee members have previously been transmitted to OHEA. We appreciate the opportunity to provide our scientific advice on this issue and request that the Agency formally respond to our letter. We stand ready to provide any further review that is requested.

Sincerely,

Herschel E. Griffin, M.D.
Chair, Environmental Health Committee

Norton Nelson, Ph.D.
Chair, Executive Committee

cc: Alvin L. Alm (A-101)
Joseph A. Cannon (ANR-443)
Bernard D. Goldstein (RD-672)
John A. Moore (TS-788)
Jack E. Ravan (WH-556)
Milton Russell (PM-219)
Lee M. Thomas (WH-562A)

TECHNICAL COMMENTS BY THE ENVIRONMENTAL HEALTH COMMITTEE

REGARDING EPA's DRAFT HEALTH ASSESSMENT DOCUMENT FOR MANGANESE

The Environmental Health Committee of EPA's Science Advisory Board has completed its review of a draft Health Assessment Document for Manganese [EPA-600/8-83/013; June, 1983; External Review Draft], which was prepared by the Office of Health and Environmental Assessment in the Office of Research and Development.

The Committee agrees with the position in the draft document that manganese can elicit pulmonary and neurologic effects in humans. The Committee questions the Agency's finding, however, that pulmonary effects occur at lower exposure levels than do neurologic effects.

The document relies too heavily on a Japanese epidemiologic study of pulmonary effects in children living near a fermomanganese processing plant. Due to confounding factors, such as the proximity of home site to the plant, other pollutants in the exhaust, passive smoking, or socioeconomic status, variables other than exposure to manganese could explain the results. The manganese exposure levels at which effects are recorded in the Japanese study appear inconsistent with the levels at which pulmonary effects were recorded in other experiments. For such reasons, the study does not provide a sufficently strong scientific basis to support the conclusions in the document. The pulmonary effects noted in these children might also be due to other compounds in the emissions.

The Committee finds that manganese is a possible mammalian mutagen according to the criteria established by the National Academy of Sciences.

Although manganese is an essential trace element, it is not clear from the literature whether inhaled manganese is available as a nutrient. Inhaled manganese may by-pass those processes by which manganese becomes available for nutrition. Data are available in humans and dogs regarding lung retention of manganese. The Agency should use these data to estimate deposition and absorption.

The Committee has various comments on the exposure sections of the draft document. A scientific explanation is needed on the choice of variables in the exposure equation given in terms of mg/day; neither is mg/day a concentration. No evidence is presented to support the concept that breathing rate determines uptake. The deposition fraction is not constant among different species. Also, body surface area is not a good basis for converting inhalation doses between species. Since lung retention can be calculated from the studies by Morrow et. al., (see reference below) the Agency can calculate lung accumulation. From this information, an equilibrium lung concentration can be estimated from ambient concentrations and particle sizes. The Committee recommends that the document provide air concentrations, rather than total uptake per time period, to the extent that the available data exist. The discussion of exposure also needs to address the effect of particle size upon uptake by inhalation. Finally, it is not clear that the term "C_A" that is used in the text is an air concentration. An explanation for this term and its use should be presented.

Human equivalent intake rate ("HEI" in the text) is equal to the amount of manganese inhaled by the experimental animal per day, corrected by a factor supposedly reflecting body surface area. Apparently, this factor is introduced to correct for differences in the fraction of manganese deposited in the respiratory tract between animals and humans. No scientific justifications are presented for the assumptions (see page A-2) that particulate matter is absorbed and retained proportional to the breathing rate, and that the retained fraction is the same for all species.

In calculating health effects associated with manganese exposures, there are two relevant dose factors. These include: 1) the dose to the lung which is determined by deposition and clearance of the inhaled manganese, and 2) the dose to the central nervous system which is based upon transfer rates from the lung. Because of unknown differences in the sensitivity of inhaled manganese between rodents and humans, the extrapolation of effects to the human lung from rat inhalation studies is speculative. Likewise, the calculation of dose to the central nervous system in the absence of data on the metabolism of inhaled manganese and the transfer rates from the lung to the central nervous system lacks scientific support.

Since it can be assumed that deposition in the lung and subsequent clearance and metabolism of manganese in primates will best resemble these processes in humans, the most relevant data is that reported in studies of nonhuman primates. Differences in particle sizes (experimental study versus ambient air) and in the chemical species of manganese have to be considered in making such comparisons. If manganese dioxide (as used in some primate studies) occurs in ambient air, for example, the dose (D) in micrograms, deposited per day in monkeys, could be estimated from the following formula:

$$D = f \cdot C \cdot V_{min} \cdot 1440,$$

where f= fractional deposition (dependent on aerodynamic particle size, in the alveolar region).

C = concentration of inhaled manganese (in micrograms per liter).

V_{min} = minute Ventilation (in liters per minute).

1440 = minutes in one day

Knowing the half-time for clearance of manganese dioxide from the lung ($T_{1/2}$ = 62 days; Morrow, 1964) one can calculate the accumulated amount (A_t) of manganese in the lung according to:

$$A_t = \frac{D}{b}(1 - e^{-bt})$$

where $b = \frac{\ln 2}{T_{1/2}} = 0.011$,

and for continuous chronic exposure at a given concentration this expression becomes:

$A_h = \frac{D}{}$ (equilibrium value in lung).

For pulmonary effects, assuming that the concentration of manganese in the lung is the same in monkeys and humans, it is possible to calculate the accumulated amount for human lungs. With the equilibrium value (A_H) of manganese in human lungs, one can further attempt to estimate an ambient exposure concentration of manganese, taking into account different fractional deposition values for the particle sizes occurring in the ambient air.

This discussion is only a general outline of an attempt to arrive at an human equivalent exposure level. Many questions, however, remain unanswered and need further evaluation, including the use of results from nonprimate species (especially rodents), manganese compounds of different chemical form, transfer rates to the brain for inhaled manganese, and alveolar compared to pulmonary dose.

The reproductive effects section is unclear and needs better organization. The Committee suggests that all information about male (versus female) exposures should be integrated into one section. Studies that lead to negative conclusions need to be addressed with more consistency. Also, the reader will be confused by evaluations of some studies that wander from reporting apparent positive results to a finding that effects were absent. The possibility of indirect effects of manganese stemming from endocrine mechanisms should be addressed.

The Committee's review of the document has highlighted one deficiency in the literature which could be remedied through research. This pertains to the correspondence in time of pulmonary and neurologic end points in response to inhaled manganese. Further research on this issue would hopefully resolve the questionable conclusion (see page 4 of the Agency's issue paper for manganese) that pulmonary effects occur at lower exposures than do neurotoxic effects.

Some additional key literature citations which the Agency should reference include:

(1) P.E. Morrow, F.R. Gibb and K. Gazioglu, "The Clearance of Dust From the Lower Respiratory of Tract of Man: An Experimental Study," in Inhaled Particles and Vapors II, C.N. Davies, ed., (1965), pp. 351-358.

(2) P.E. Morrow, F.R. Gibb and L. Johnson, "Clearance of Insoluble Dust From the Lower Respiratory Tract," Health Physics, 10 (1964), 543-555.

In addition, Dr. Weiss provided OHEA with a reference to a paper by Van Bogaert & Dallemagne that represents the first study of manganese inhalation with primates.

The Appendix to the document, which discusses various issues related to Acceptable Daily Intake (ADI) levels for manganese, should be revised or deleted. OHEA may wish to follow-up with individual Committee members to review their concerns over the conversion of ADI's using various routes of administration as well as other issues.

ATTACHMENT C-1

Sky-Peck (1990)

Clin Physiol Biochem 1990;8:70–80

0252–1164/90/0082–0070$2.75/0

Distribution of Trace Elements in Human Hair

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Key Words. Human hair · Trace elements · X-ray fluorescence · Hair treatment · Age · Sex · Race · Environment

Abstract. Scalp hair has been successfully used in forensic medicine, screening populations for heavy metal poisoning, and for monitoring environmental pollutants. However, its use for the diagnosis of the individual for disease or nutritional status has been questionable. This is primarily due to the large individual differences associated with age, sex, race, hair color, hair treatment, and environmental exposure.

Introduction

Considerable interest has been shown in the past 10 years in the analysis of trace elements in human hair. It has become increasingly popular for the evaluation of systemic intoxication, for predictions of exposure to environmental pollutants, for the assessment of nutritional status, and for the diagnosis of disease states. The popularity of hair as a tissue specimen resides, in part, in the ease with which samples can be obtained without pain or trauma to the individual, important when sampling large populations, and in the relative stability of specimens which require no special equipment or storage conditions except to prevent postsampling contamination [1–3].

These properties, coupled with the sensitivity of newer analytical techniques, including atomic absorption, neutron activation, and X-ray fluorescence, have been partly responsible for this current surge of applied research on trace elements in hair. In spite of these advantages, the ranges of values reported for many of the trace elements found in hair have varied widely. The reasons for this include sampling techniques, sample preparation, external contamination arising from hair treatment such as shampoos, cosmetic preparations, and atmospheric fallout.

The present study was undertaken to determine the extent to which these various parameters affect the wide range of values found in a population of healthy individuals. These included age, sex, race, hair color, hair treatment, and environmental contamination. Not included in this study were the effects of smoking [4] and oral contraceptives [5].

Materials and Methods

Scalp hair was generously donated by 987 healthy individuals of both sexes, ranging in age from 3 to 70 years. These individuals were primarily employees of the Rush Presbyterian-St. Luke's Medical Center, Chicago, or family members. All individuals lived in Cook County, Ill. Six strands of hair were obtained from the crown of the head of each individual. Hair was pulled out with the root and stored in 10 × 15-cm polyethylene zipper-locked bags.

One of the problems encountered in the use of scalp hair for trace element analysis has been external contamination which may arise from application of shampoo, water used for hair washing, cosmetic preparation, and atmospheric fallout. At present there is no standard procedure established for the collection and preparation of hair samples for trace metal analysis [6]. Many authors have suggested that hair samples be washed prior to analysis. However, the washing procedure to which hair is subjected should remove only the external contaminations and not internal metal ions. Various washing techniques have been reported and range from no washing at all [7] and the use of only distilled water [8] to various ethylenediaminetetraacetic acid solutions [9] and various detergents plus solvents [10] or only solvents [11]. The procedure adopted for the present study was a mild detergent, an isopropanol rinse, followed by a distilled water rinse. Prior to analysis the hair was washed in an anionic detergent (1% sodium lauryl sulfate), distilled water, isopropanol, distilled water and air-dried in a laminar flow hood. The dried strands of hair, oriented in the same direction according to the root, were suspended as a bundle of parallel unidirectional strands across a 5 × 5-cm Lucite plastic holder containing a centered 2.5-cm hole and held in place by a 2.5-cm Teflon ring. This simple holder made possible serial determinations of trace elements along the length of the hair with minimal risk of contamination. The mounted samples were placed in the sample chamber of the energy-dispersive X-ray fluorescence (EDXRF) system which was then air-evacuated prior to analysis.

This quantitative EDXRF system has been developed for the rapid simultaneous multielement analysis of microsamples. When excited by an appropriate source, a sample will emit X-rays of discrete energies that are characteristic for the elements composing the sample. By measuring the energies of X-rays emitted from the excited sample and counting the number of X-rays of each energy, the EDXRF system allows the identification and quantification of the elements present in the sample. The entire system, including excitation source, pulse processor, silicon-drifted lithium detector, and computer system, was obtained from Kevex, (Foster City, Calif., USA). The principles and description of the EDXRF system have previously been described by Sky-Peck and Joseph [12, 13].

In order to quantitate the energy emission peaks for the various elements in hair and to establish a

Table 1. Effect of hair washing on the distribution of trace elements[a]

	Unwashed[b]	Washed[b]	p[c]
Sulfur (mg/g)	40.5 ± 7.3	42.3 ± 8.0	0.55
Calcium	550 ± 348	402 ± 296	0.25
Iron	19.3 ± 5.9	18.8 ± 5.2	0.18
Nickel	1.15 ± 0.82	1.22 ± 0.51	0.82
Copper	21.8 ± 5.1	21.3 ± 6.3	0.80
Zinc	171.7 ± 59.2	150.0 ± 58.5	0.35
Selenium	0.61 ± 0.34	0.62 ± 0.27	0.95
Bromine	4.90 ± 4.10	3.30 ± 2.20	0.25
Strontium	18.9 ± 23.0	17.1 ± 22.6	0.85
Chromium	1.56 ± 0.74	1.60 ± 0.49	0.85
Manganese	1.55 ± 1.19	1.41 ± 1.02	0.25
Arsenic	0.55 ± 0.54	0.55 ± 0.50	1.00
Mercury	1.17 ± 0.74	1.20 ± 0.94	0.90
Lead	6.41 ± 4.40	5.96 ± 4.92	0.82
Rubidium	0.98 ± 0.58	0.78 ± 0.47	0.80

[a] Analysis of identical hair samples before and after washing with detergent, distilled water, and isopropanol.

[b] Mean ± SD of samples from 24 individuals (μg/g dry weight).

[c] Student's t distribution and chi-square probability.

calibration file of elements for computer storage. internal standards of each element under investigation were added to a protein solution similar in composition to that of hair. Five micrograms per milliliter of solution was added in groups such that there was no interference between elements. The element standards used were calcium, titanium, vanadium, chromium, manganese, iron, nickel, copper, zinc, arsenic, selenium, bromine, rubidium, strontium, yttrium, zirconium, molybdenum, mercury, and lead, to cover the entire energy range of 0–22 keV. Five-microliter aliquots of these standard solutions were dried on Formvar films and analyzed under the same conditions employed for hair. Prior to the analysis of the area of each peak and quantitative determination of the elements present in the sample, the effects of background scatter were subtracted directly from the acquired spectra by computer.

Results

Prior to the initiation of the present study, identical strands of hair, obtained from 24 individuals, were analyzed before and after washing as described in Materials and Methods. The results of this washing are presented in table 1. These results show that

Table 2. Mean distribution (± SD) of trace elements in hair according to sex (μg/g dry weight)

	Males (n = 455)	Females (n = 512)	p[a]
Sulfur (mg/g)	38.2 ± 6.4	36.1 ± 6.4	0.014
Calcium	501.4 ± 394.0	1,280 ± 1,130.5	0.0001
Iron	14.1 ± 10.3	11.5 ± 9.9	0.043
Nickel	0.76 ± 0.76	1.09 ± 1.10	0.005
Copper	19.90 ± 9.8	23.9 ± 16.2	0.025
Zinc	189.1 ± 39.3	194.4 ± 43.2	0.023
Selenium	0.72 ± 0.32	0.58 ± 0.23	0.0004
Bromine	4.40 ± 3.60	2.14 ± 1.81	0.0001
Strontium	6.40 ± 12.40	6.50 ± 6.10	0.47
Chromium	1.16 ± 0.66	1.01 ± 0.62	0.56
Manganese	1.14 ± 0.65	1.17 ± 1.27	0.43
Arsenic	0.50 ± 0.61	0.38 ± 0.80	0.13
Mercury	1.03 ± 2.40	0.89 ± 0.58	0.28
Lead	12.44 ± 15.01	7.25 ± 11.80	0.005
Rubidium	0.74 ± 0.33	0.74 ± 0.40	1.00

[a] Student's t distribution and chi-square probability.

the mild hair washing used in this investigation had no statistically significant effect on the levels of trace metals found in the hair. On the other hand, commercially available shampoos which contain chelating agents caused the release of significant amounts of calcium and iron.

There were significant differences in the distribution of trace elements in hair with respect to sex, as seen in table 2. The sulfur, iron, and selenium contents were lower in females, while calcium, nickel, copper, and zinc levels were significantly elevated. However, some of these differences such as in sulfur, calcium, nickel, and zinc may in part actually reflect hair treatment by women. Some of these effects of hair treatment are presented in table 3. Both peroxide bleaches and permanent-wave mixtures markedly altered the contents of sulfur, calcium, iron, and nickel in hair. In addition, peroxide affected zinc levels, and permanent waving increased copper and arsenic levels. These changes due to hair treatment not only complicate the interpretation of results due to sexual difference, but also nutritional interpretations.

Table 3. Mean distribution (± SD) of trace elements in hair according to hair treatment (females; μg/g dry weight)

	Natural (n = 86)	Peroxide (n = 67)	p	Permanent (n = 54)	p[a]
Sulfur (mg/g)	36.8 ± 4.9	31.0 ± 4.8	0.006	40.7 ± 6.7	0.02
Calcium	986 ± 643	2,019 ± 1,446	0.0004	2,358 ± 2,235	0.0003
Iron	11.6 ± 5.4	8.1 ± 2.3	0.03	14.7 ± 6.2	0.05
Nickel	0.70 ± 0.48	0.68 ± 0.26	0.31	3.18 ± 1.5	0.0001
Copper	21.4 ± 7.1	20.1 ± 11.5	0.33	26.0 ± 5.6	0.02
Zinc	194.6 ± 39.6	124.9 ± 83.3	0.0001	210.6 ± 43.3	0.12
Selenium	0.55 ± 0.18	0.37 ± 0.12	0.35	0.53 ± 0.16	0.37
Bromine	2.15 ± 1.8	1.42 ± 0.37	0.11	1.96 ± 0.21	0.36
Strontium	5.69 ± 4.0	5.56 ± 5.36	0.46	5.50 ± 3.10	0.45
Chromium	0.99 ± 0.42	0.89 ± 0.31	0.25	0.96 ± 0.29	0.41
Manganese	1.13 ± 0.56	0.95 ± 0.68	0.30	1.34 ± 0.41	0.12
Arsenic	0.33 ± 0.44	0.19 ± 0.14	0.17	0.81 ± 0.47	0.001
Mercury	0.87 ± 0.48	1.09 ± 0.79	0.13	0.70 ± 0.44	0.14
Lead	5.51 ± 5.97	3.87 ± 3.70	0.21	8.1 ± 5.4	0.08
Rubidium	0.74 ± 0.41	0.53 ± 0.24	0.07	0.63 ± 0.32	0.20

[a] Student's t distribution and chi-square probability.

Differences in natural hair color also played a significant role in the interpretation of the normal distribution of trace element values. Comparisons between female natural blonds, brunettes, and redheads are shown in table 4. Blonds had significantly less iron and manganese than brunettes, while redheads had more chromium, copper, and zinc [illegible] and oriental females indicated some statistically significant differences in trace element concentration between the races. These are present in table 5. Striking differences between Caucasians and blacks were found with increased levels of calcium, iron, nickel, chromium, manganese, arsenic, and lead in blacks. Here again, some of these apparent racial differences may in part be a reflection of hair treatment and environmental exposure.

Separating individuals according to age groups, 3–20 and 58–70 years, indicated a [illegible] zinc, selenium, and strontium content with the older age group. Contrary to the findings of Nechay and Sunderman [14], nickel was

Table 4. Mean distribution (± SD) of trace elements according to hair color (females; µg/g dry weight)

	Brunettes (n = 32)	Blonds (n = 30)	p	Redheads (n = 30)	p[a]
Sulfur (mg/g)	36.8 ± 5.3	35.8 ± 3.7	0.29	38.5 ± 4.5	0.16
Calcium	953.6 ± 778.6	768.0 ± 462.3	0.23	937.4 ± 686.7	0.48
Iron	9.6 ± 2.4	7.6 ± 1.4	0.007	17.8 ± 6.8	0.0001
Nickel	0.53 ± 0.26	0.44 ± 0.20	0.15	0.75 ± 0.35	0.02
Copper	17.3 ± 4.2	17.2 ± 3.6	0.47	24.2 ± 8.2	0.0014
Zinc	187.9 ± 39.0	181.4 ± 38.3	0.33	211.8 ± 32.1	0.03
Selenium	0.58 ± 0.21	0.53 ± 0.15	0.30	0.55 ± 0.19	0.33
Bromine	1.64 ± 0.88	1.53 ± 0.61	0.41	1.25 ± 0.69	0.08
Strontium	5.25 ± 3.30	3.80 ± 1.4	0.08	5.35 ± 3.15	0.45
Chromium	1.12 ± 0.43	0.90 ± 0.44	0.09	0.95 ± 0.41	0.12
Manganese	1.03 ± 0.54	0.72 ± 0.31	0.04	1.18 ± 0.54	0.21
Arsenic	0.30 ± 0.61	0.30 ± 0.25	1.00	0.39 ± 0.48	0.32
Mercury	1.00 ± 0.56	0.99 ± 0.58	0.31	0.63 ± 0.31	0.01
Lead	3.44 ± 2.90	6.60 ± 5.70	0.03	4.80 ± 3.56	0.11
Rubidium	0.79 ± 0.39	0.72 ± 0.35	0.44	0.70 ± 0.48	0.27

[a] Student's t distribution and chi-square probability.

significantly elevated with age in this population. The results are presented in table 6.

In addition, comparisons were made between natural color hair and gray hair obtained from the same individuals. These data, obtained from 146 individuals, as shown in table 7, were subjected to paired analysis by the Student's t test. There are no significant differences in the trace metal content of natural or gray hair obtained from the same individual.

Long strands of hair, obtained from 16 healthy young ladies whose only hair treatment was shampoo and brushing, were serially analyzed at 2.5-cm intervals, starting at the root. The results, similar to those reported by Valkovic et al. [15] and Yukawa et al. [16], are shown in figure 1. The elements zinc, copper, iron, selenium, and sulfur were relatively constant throughout the hair length; lead, nickel, manganese, calcium, and strontium significantly increased in concentration as a function of distance from the root. These changes with length were interpreted to indicate environmental exposure as a function of time which was

Table 5. Mean distribution (± SD) of trace elements in hair according to race (females; μg/g dry weight)

	Caucasian (n = 86)	Black (n = 60)	p	Oriental (n = 45)	p[a]
Sulfur (mg/g)	36.8 ± 4.9	32.5 ± 8.7	0.005	36.5 ± 4.3	0.41
Calcium	986.3 ± 642.8	1,550 ± 1,132.2	0.005	468.2 ± 267	0.002
Iron	11.6 ± 5.4	20.9 ± 9.9	0.0001	7.5 ± 2.0	0.002
Nickel	0.70 ± 0.48	2.16 ± 1.50	0.0001	0.45 ± 0.19	0.03
Copper	21.4 ± 7.1	21.8 ± 11.2	0.43	15.4 ± 5.4	0.002
Zinc	194.6 ± 39.6	181.8 ± 68.9	0.16	197.6 ± 33.0	0.39
Selenium	0.55 ± 0.18	0.62 ± 0.29	0.37	0.65 ± 0.21	0.04
Bromine	2.15 ± 1.80	2.49 ± 1.37	0.21	1.87 ± 1.0	0.28
Strontium	5.69 ± 4.00	6.73 ± 5.10	0.17	3.3 ± 2.3	0.03
Chromium	0.99 ± 0.42	1.48 ± 0.71	0.0003	0.88 ± 0.29	0.17
Manganese	1.13 ± 0.56	1.68 ± 1.05	0.003	0.68 ± 0.36	0.002
Arsenic	0.33 ± 0.44	1.10 ± 1.58	0.002	0.15 ± 0.18	0.07
Mercury	0.87 ± 0.48	0.40 ± 0.44	0.0001	0.81 ± 0.45	0.33
Lead	5.51 ± 5.97	28.40 ± 32.40	0.0001	1.56 ± 1.47	0.005
Rubidium	0.74 ± 0.41	0.51 ± 0.24	0.008	0.66 ± 0.38	0.24

[a] Student's t distribution and chi-square probability.

not easily removed by mild washing prior to analysis.

The concentration of lead and strontium in the hair of those individuals living in the Greater Metropolitan area of Chicago were grouped according to residence by zip code. Individuals who lived in the city and used lake water had a much higher lead to strontium ratio than individuals who lived in the suburbs and used well water which contained higher strontium levels compared to lake water. Those individuals living near large industrial complexes, as Gary, Ind., USA, or in older communities, where lead plumbing and lead-based paint exist, had higher levels of lead than those living in non-industrial residential communities. The distribution of lead and strontium in hair according to location of residence in the Greater Metropolitan Chicago area can be seen in figure 2. These results are similar to those reported by Creason et al. [4] in Metropolitan New York and by Chatt et al. [17] in Toronto, Ont., Canada.

During the course of the present study it was noted that certain individuals had exces-

Table 6. Mean distribution (± SD) of trace elements in hair as a function of age (μg/g dry weight)

	Age groups		p[a]
	3–20 years (n = 60)	58–70 years (n = 60)	
Sulfur (mg/g)	37.5 ± 4.4	31.9 ± 4.4	0.007
Calcium	600.9 ± 220.0	298.1 ± 190.5	0.003
Iron	10.4 ± 3.6	10.5 ± 1.9	0.47
Nickel	0.46 ± 0.24	0.76 ± 0.38	0.02
Copper	18.3 ± 5.5	17.3 ± 5.3	0.15
Zinc	187.3 ± 39.4	172.1 ± 46.8	0.02
Selenium	0.62 ± 0.18	0.56 ± 0.14	0.03
Bromine	1.49 ± 0.93	6.80 ± 4.7	0.04
Strontium	3.13 ± 0.92	1.78 ± 0.81	0.0001
Chromium	1.03 ± 0.43	1.21 ± 0.63	0.23
Manganese	0.89 ± 0.37	1.04 ± 0.40	0.22
Arsenic	0.25 ± 0.23	0.34 ± 0.26	0.21
Mercury	0.63 ± 0.37	0.51 ± 0.19	0.26
Lead	4.10 ± 2.9	16.10 ± 12.5	0.003
Rubidium	0.61 ± 0.28	1.19 ± 0.81	0.02

[a] Student's t distribution and chi-square probability.

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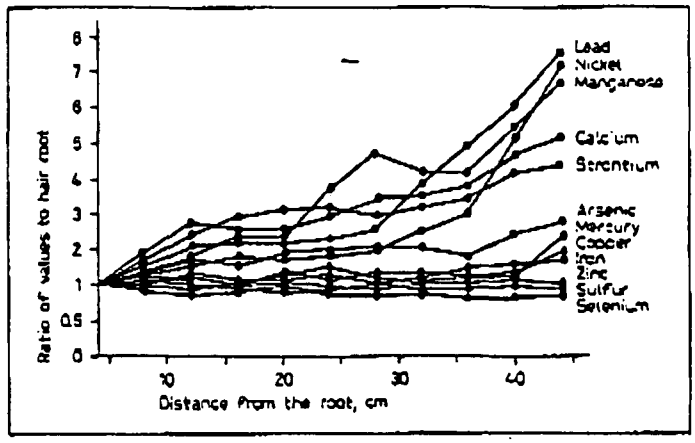


Fig. 1. Distribution of trace elements as a function of hair length.

Table 7. Mean distribution (± SD) of trace elements in hair – comparison of natural color to gray (μg/g dry weight)[a]

	Male natural (n = 73)	Male gray (n = 73)	p	Female natural (n = 73)	Female gray (n = 73)	p[b]
Sulfur (mg/g)	38.2 ± 6.4	36.2 ± 5.8	0.16	36.1 ± 6.4	38.2 ± 7.6	0.17
Calcium	501.4 ± 394	331.9 ± 270.1	0.08	1,280.8 ± 1,130.5	1,141.3 ± 730.4	0.45
Iron	14.1 ± 10.3	9.4 ± 2.4	0.06	11.5 ± 9.9	15.2 ± 9.0	0.13
Nickel	0.76 ± 0.76	0.67 ± 0.46	0.30	1.09 ± 1.10	1.45 ± 0.83	0.16
Copper	19.90 ± 9.8	16.10 ± 4.5	0.09	23.9 ± 16.2	22.4 ± 9.7	0.39
Zinc	181.9 ± 39.3	181.6 ± 40.3	1.00	191.4 ± 43.2	189.9 ± 24.7	0.37
Selenium	0.72 ± 0.32	0.60 ± 0.21	0.11	0.58 ± 0.23	0.61 ± 0.34	0.36
Bromine	4.40 ± 3.60	5.91 ± 4.39	0.10	2.14 ± 1.81	1.76 ± 0.94	0.26
Strontium	6.40 ± 12.40	2.78 ± 2.47	0.16	6.50 ± 6.10	8.18 ± 7.70	0.21
Chromium	1.16 ± 0.66	1.38 ± 0.87	0.16	1.01 ± 0.62	1.00 ± 0.56	0.48
Manganese	1.14 ± 0.65	1.35 ± 0.68	0.16	1.17 ± 1.27	1.45 ± 1.58	0.26
Arsenic	0.50 ± 0.61	0.36 ± 0.43	0.23	0.38 ± 0.80	1.10 ± 0.08	0.14
Mercury	1.03 ± 2.40	0.60 ± 0.22	0.27	0.89 ± 0.58	1.00 ± 0.42	0.28
Lead	12.44 ± 15.01	11.40 ± 9.20	0.41	7.25 ± 11.80	2.81 ± 1.60	0.12
Rubidium	0.74 ± 0.3	0.86 ± 0.36	0.13	0.74 ± 0.40	0.96 ± 0.51	0.06

[a] Comparison of male and female populations with individuals with gray hair.
[b] Student's t distribution and chi-square probability.

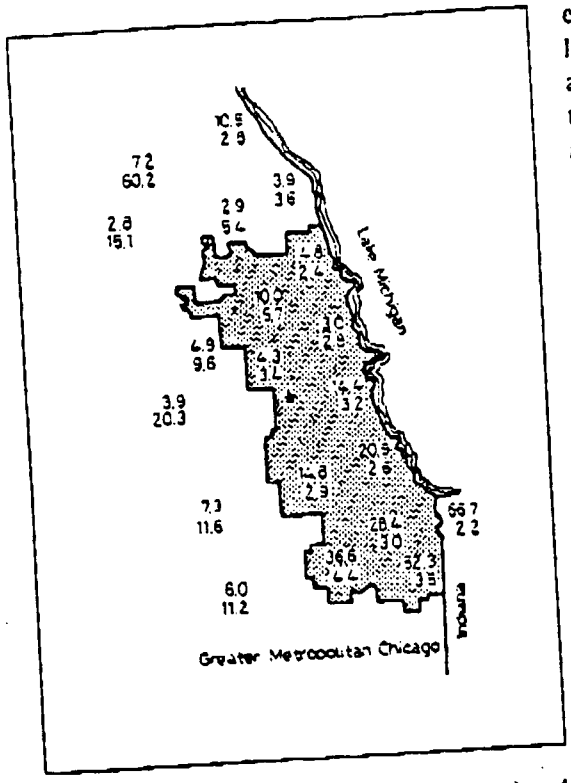


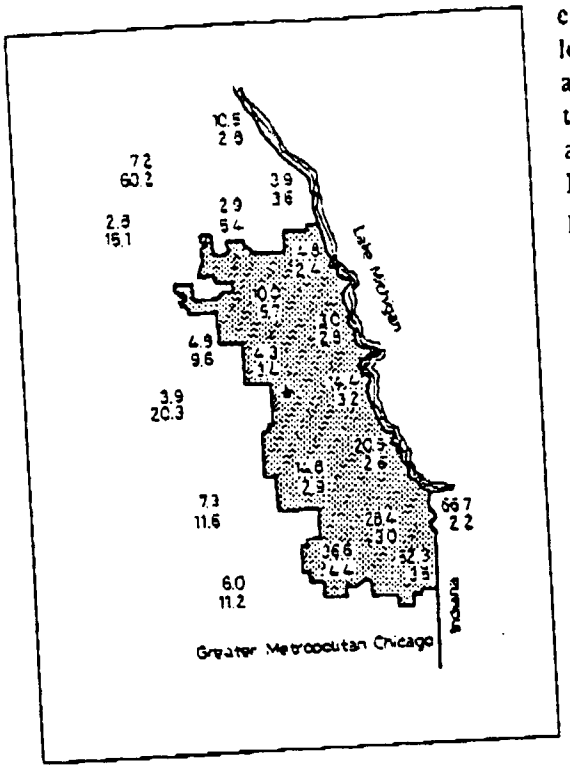
Fig. 2. Distribution of lead (upper figures) and strontium (lower figures) according to residence in Greater Metropolitan Chicago. The asterisk indicates location of Rush Presbyterian-St.Luke's Medical Center.

sively high levels of hair lead, ranging in concentrations from 60 to 680 μg/g. Some of these individuals were plumbing and maintenance personnel. However, further investigation revealed that Grecian Formula, a lead acetate containing hair dye, was being used by some males with graying hair. A comparison analysis of blood lead levels between this group ($n = 26$) and a group of males with normal hair lead levels ($n = 79$) indicated the normal blood level to be 11 ± 9, while the blood level in the high-lead hair group was 16 ± 8 with a statistical significant difference of $p < 0.01$. While these elevated lead levels may be considered subclinical or asymptomatic for lead intoxication [18], they have been linked to nervous system alterations, neurochemical alterations, lower IQ scores, behavioral disorders [19], and hypertension [20] in the general population.

Discussion

Despite the many drawbacks, hair analysis has been successfully used in forensic medicine, as a screening tool for the detection of heavy metal poisoning, and for monitoring levels of environmental pollutants. According to the US Environmental Protection Agency [21] hair analysis is an effective screening test system for toxic heavy metal contamination, especially for lead, arsenic, cadmium, and mercury. The authors conclude that hair may be a more convenient way to study a community exposure than the analysis of blood or urine.

From the results presented above, it is obvious that there are wide variations in the distribution of trace metals in hair. This is due to many factors, among which are age, sex, race, glandular secretions, and especially environmental exposure, e.g., cosmetics, aerosols, detergents, bleaches, dyes, and shampoos. Even the essential trace elements sulfur, iron, copper, zinc, and selenium, which appear to be relatively consistent throughout the hair length (fig. 1), show wide variations when analyzed as absolute values (table 2). Thus the composition of hair is not only determined by incorporation of trace elements from the bloodstream, but by external factors from the environment, as shown by Ryabukhin [3], McKenzie [22], and Abraham [23].



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Unfortunately, in recent years a number of self-styled nutritional authorities and several commercial laboratories have touted hair analysis for the diagnosis of nutritional status of individuals and have openly solicited mail-order analysis of hair samples. On the basis of their results, often on inappropriate samples and inadequate histories, these practitioners have prescribed elaborate vitamin and mineral dietary supplements or chelation therapy in the case of excess trace metals [2]. Such analyses provide numerical results of very little value which are frequently used to support questionable diagnoses based on the assumption that hair analysis alone is a diagnostic rather than a screening test.

However, if used in conjunction with other clinical information and laboratory tests, hair analyses may become a useful screening tool for the determination of certain nutritional disorders and chronic diseases. Its usefulness at present is questionable due to a lack of knowledge about the many factors which influence the distribution of trace elements in hair. Until more studies are conducted, and the role of essential trace elements and the effect of environmental factors on human health and disease evaluation of an individual's metabolic state will remain experimental as well as controversial.

References

1 Katz SA: The use of hair as a biopsy material for trace elements in the body. Am Lab 1979;11:44–52.

2 Fletcher DJ: Hair analysis: Proven and problematic applications. Postgrad Med 1982;72:79–88.

3 Ryabukhin YS: International coordinated program on activation analysis of trace element pollutants in human hair; in Brown AC, Craunse RG (eds): Hair, Trace Elements and Human Illness. New York, Praeger, 1980, pp 3–44.

4 Creason JP, Hinners TA, Bumgarner JE, et al: Trace elements in hair as related to exposure in Metropolitan New York. Clin Chem 1975;21: 603–612.

5 Deeming JP, Weber CW: Hair analysis of trace minerals in human subjects as influenced by age, sex, and contraceptive drugs. Am J Clin Nutr 1978;31:1175–1180.

6 Cranton EM, Bland JS, Chatt A, et al: Standardization and interpretation of human hair for elemental concentrations. J Holistic Med 1982;4:10–20.

7 Smith H: The interpretation of ash content of human hair. J Forensic Sci Soc 1964;4:192–196.

8 Rabinowitz M, Wetherill G, Kopple J: Delayed appearance of trace lead in facial hair. Arch Environ Health 1976;31:220–223.

9 Clark AN, Wilson DJ: Preparation of hair for lead analysis. Arch Environ Health 1974;28:292–296.

10 Harrison WW, Yurachek JR, Benson CA: Determination of trace elements in human hair by atomic absorption spectrophotometry. Clin Chim Acta 1969;23:82–91.

11 Petering HG, Yeager DW, Witherup SO: Trace metal content of hair. Arch Environ Health 1971; 23:202–207.

12 Sky-Peck HH, Joseph BJ: Determination of trace elements in human serum by energy dispersive X-ray fluorescence. Clin Biochem 1981;14:126–131.

human hair in trace metal analysis; in Brawn SS, Savory J (eds): The Clinical Chemistry and Chemical Toxicology of Trace Metals. London, Academic Press, 1983, pp 281–286.

14 Nechay MW, Sunderman FW Jr: Measurement of nickel in hair by atomic absorption spectrophotometry. Ann Clin Lab Sci 1973;3:30–35.

15 Valkovic V, Rendic D, Phillips GC: Element ratios along human hair as an indicator of exposure to environmental pollutants. Environ Sci Tech 1975;9:1150–1152.

16 Yukawa M, Suzuki YM, Tanaka S: The variations of trace element concentration in human hair: The trace element profile in human long hair by sec-